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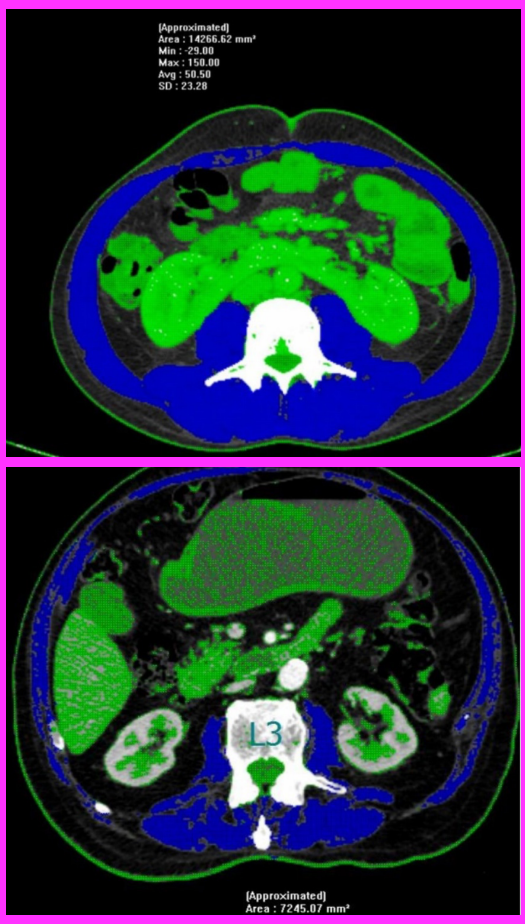

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4. The file size should be a maximum of 100 MB.

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6. Main text should not exceed 500 words.

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8. Video and images must be cited within main text.

9. There should be no identification of patient / physician / institution / city / country in pictures and especially video images.

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Books with Single Author: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

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Original Articles

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EDITORIAL

Dear Readers;

I am very happy to be with you with our new issue in the new year. In this issue, we are together with you with valuable works.

We took the cover art for this issue from the study "Sarcopenia is Associated with Postoperative Complications in Patients Undergoing D2 Gastrectomy for Gastric Cancer" by Alemdar et al. Sarcopenia is associated with early postoperative complications in many types of cancer. In this study, the relationship between sarcopenia and early postoperative complications in patients who underwent curative D2 lymph node dissection for gastric cancer was investigated. The postoperative complication rate in sarcopenic patients was higher than in non-sarcopenic patients, the rate of surgical and medical complications was higher in sarcopenic patients, and the rate of serious surgical complications was significantly higher in the sarcopenia group. It was concluded that the use of CT in the preoperative clinical staging of the patients and taking the necessary precautions facilitated the management of postoperative complications.

Other articles we have chosen for you in this issue are:

"Ivermectin Induces Oxidative Stress and DNA Damage in Breast Cancer Cells" by Güler et al., "Comparative Analysis of Tertiary Stroke Center: Factors Affecting the 3rd Month Clinical Outcome of Patients Treated with Thrombolytic Treatment" by Karadeli et al., "Evaluation of the Relationship Between Maxillary Labial Frenulum Attachment Types, Periodontal Health, and Dental Caries in Preschool Children" by Taran et al.

Dear Readers,

It's hard not to be happy when you see the efforts of healthcare professionals for scientific studies under heavy workload in our country and the efforts made for an academic career.

On this occasion, I congratulate your new year and wish it to be a blessing for our country and the world.

Kind regards,
Prof. Dr. Adem AKÇAKAYA
Editor in Chief

Original Article

DOI: 10.14235/bas.galenos.2022.53325
Bezmialem Science 2023;11(1):1-7

Morphometric Analysis of the Foramen Palatinum Majus by Cone-beam Computed Tomography

Foramen Palatinum Majus'un Konik Işınlı Bilgisayarlı Tomografi ile Morfometrik Analizi

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ABSTRACT

Objective: The aim of this study was to detect possible variations of the foramen palatinum majus (FPM), by imaging with cone-beam computed tomography (CBCT), and to make a morphometric comparison of FPM in dentate and edentulous individuals.

Methods: In the study, CBCT recordings of 250 individuals, 125 dentate and 125 edentulous individuals, in the archive of the Faculty of Dentistry, Oral and Maxillofacial Radiology were retrospectively analyzed. The diameter of the FPM, its position relative to the molar teeth, its shape (round, ovoid, slit), its distance from the mid-maxillary suture (MMS), and its distance from the incisive foramen (IF) were evaluated. The SPSS V.21 software (IBM Corp., Armonk, NY, USA) was used for the analysis of the data and it was considered significant at the $p<0.05$ level.

Results: The records of 122 female and 128 male patients aged between 18 and 86 years (52±16) were examined. In dentate individuals, FPM was most frequently located in the region between the second and third molars, 54.4% on the right and 56.8% on the left. The most common FPM shape was ovoid, with 80% on the right and 74.4% on the left. The diameter of FPM, FPM-MMS, and FPM-IF distance showed a statistically significant difference between dentate and edentulous individuals, and the values of edentulous individuals were higher ($p<0.05$).

Conclusion: Since the position of the FPM in the maxilla changes with tooth loss, dentists should be careful in surgical and anesthesia procedures in this region.

Keywords: Greater palatine foramen, maxilla, cone-beam computed tomography

ÖZ

Amaç: Bu çalışmanın amacı, foramen palatinum majusun (FPM) konik ışınlı bilgisayarlı tomografi (KIBT) ile görüntülenerek olası varyasyonlarının tespiti, dişli ve dişsiz bireylerde FPM'nin morfometrik karşılaştırmasının yapılmasıdır.

Yöntemler: Çalışmada Diş Hekimliği Fakültesi Ağız, Diş ve Çene Radyolojisi arşivinde bulunan 125 dişli ve 125 dişsiz toplam 250 bireye ait KIBT kayıtları retrospektif olarak incelenmiştir. FPM'nin çapı, molar dişlere göre konumu, şekli (yuvarlak, ovoid, yarık), mid-maksiller sütur (MMS) ve insiziv foramene (İF) olan mesafesi değerlendirilmiştir. Verilerin analizi için SPSS V.21 yazılımı (IBM Corp., Armonk, NY, USA) kullanılmış olup $p<0,05$ seviyesinde anlamlı kabul edilmiştir.

Bulgular: Çalışmada 18-86 yaş aralığında (52±16), 122 kadın ve 128 erkek hastaya ait kayıtlar incelenmiştir. Dişli bireylerde FPM sağda %54,4, solda %56,8 oranında olmak üzere en sık ikinci ve üçüncü molarlar arasındaki bölgede yerleşim göstermiştir. En sık gözlemlenen FPM şekli sağda %80, solda %74,4 oranında olmak üzere ovoiddir. FPM'nin çapı, FPM-MMS ve FPM-İF mesafesi dişli ve dişsiz bireylerde istatistiksel olarak anlamlı fark göstermiş olup, dişsiz bireylerde bu değerler daha yüksektir ($p<0,05$).

Sonuç: Diş kaybı ile birlikte FPM'nin maksilladaki konumunun değişim göstermesi nedeni ile diş hekimleri bu bölgedeki cerrahi işlemler ve anestezi prosedürlerinde dikkatli davranmalıdır.

Anahtar Sözcükler: Foramen palatinum majus, maksilla, konik ışınlı bilgisayarlı tomografi

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Introduction

The foramen palatinum majus (FPM) carries the greater palatine vessels extending from the maxillary artery and the greater palatine nerve, a branch of the maxillary division of the trigeminal nerve (1). The greater palatine nerve leaves the pterygopalatine ganglion and passes through the greater palatine canal to reach the FPM in the hard palate (2). Accurate determination of the anatomical location of the FPM is very important in dentistry in procedures such as posterior palatal block anesthesia, cleft palate treatment (palatorraphy), periodontal surgery, palatal tumor resection, and palatal abscess incision (3). Maxillary nerve block anesthesia is used in the presence of odontogenic infection where infiltration anesthesia is contraindicated, and in maxillary sinus surgeries, and surgical applications where general anesthesia is contraindicated (4). With this technique, the entire hemimaxilla including the teeth, palatal and gingival mucosa, midface skin, maxillary sinus, and nasal cavity are anesthetized (5).

In a meta-analysis including 23 studies conducted by Tomaszewska et al. (6), it was stated that FPM was most frequently located opposite the maxillary third molar. It was stated that the mid-maxillary suture (MMS), posterior nasal spine (PNS), and alveolar bone were the most important points in determining the position of the FPM in edentulous patients.

In studies conducted to date, it has been reported that the position of FPM may vary according to age, gender, and racial differences (4), but the effect of tooth loss has not been sufficiently discussed. The aim of this study was to detect possible variations of FPM by imaging with cone-beam computed tomography (CBCT), and to make a morphometric comparison of FPM in dentate and edentulous individuals.

Methods

Sample and Study Design

This study was carried out retrospectively using CBCT records obtained between 2014 and 2021 at the Faculty of Dentistry, Department of Oral and Maxillofacial Radiology. The study protocol was approved by the Faculty of Dentistry Non-Pharmaceutical and Medical Device Research Ethics Committee (no: 09-79, date: 06.09.2021) and was conducted in accordance with the principles defined in the Declaration of Helsinki, including all revisions.

In the study, CBCT records of individuals over the age of 18 were examined. Artifact-free images with optimal image quality where the maxilla could be clearly examined, and CBCT recordings obtained with 100x100 mm, 140x100 mm, 170x120 mm imaging volume (field of view size) where both FPMs could be fully observed, were included in the study. CBCT records of patients with severe malocclusion and craniofacial anomalies, cleft lip-palate, orthognathic surgery, and maxillofacial trauma were excluded from the study.

Individuals without maxillary molar tooth loss were evaluated in the "dentate" group and individuals without maxillary molar teeth in the "edentulous" group.

Radiological Assessment

1. Transverse diameter of right-left FPM in axial sections (Figure 1),

2. The distance from the center of the FPM to the incisive foramen (FPM-IF), the distance from the center of the FPM to the posterior nasal spine (FPM-PNS), the closest perpendicular distance of the center of the FPM to the mid-maxillary suture in axial sections (FPM-MMS) (Figure 2),

3. The relationship of FPM to the upper molars [2nd molar level (M2), between the 2nd-3rd molars (M2-M3), at the level of the 3rd molar (M3), at the distal of the 3rd molar (D-M3)],

4. The shape of right-left FPM: round (Figure 3), ovoid (Figure 4), slit (Figure 5)

Image Acquisition

All scanning parameters were obtained with the Morita 3D Accuitomo 170 (J Morita MFG Corp. Kyoto, Japan) CBCT device according to the manufacturer's recommended protocol. Studies were conducted using i-Dixel software (J Morita MFG Corp., Kyoto, Japan). A 2.66 GHz Intel Xeon PC with 3.25 Gb RAM, Windows XPTM Professional operating system, and a 27-inch flat-panel color display (Dell U2711HTM) with a resolution of 2,560×1,600 pixels was used to analyze the CBCT images.

Statistical Analysis

The SPSS V.21 software (IBM Corp., Armonk, NY, USA) was used for data analysis. The same researchers took the measurements and repeated them twice to ensure measurement reliability and

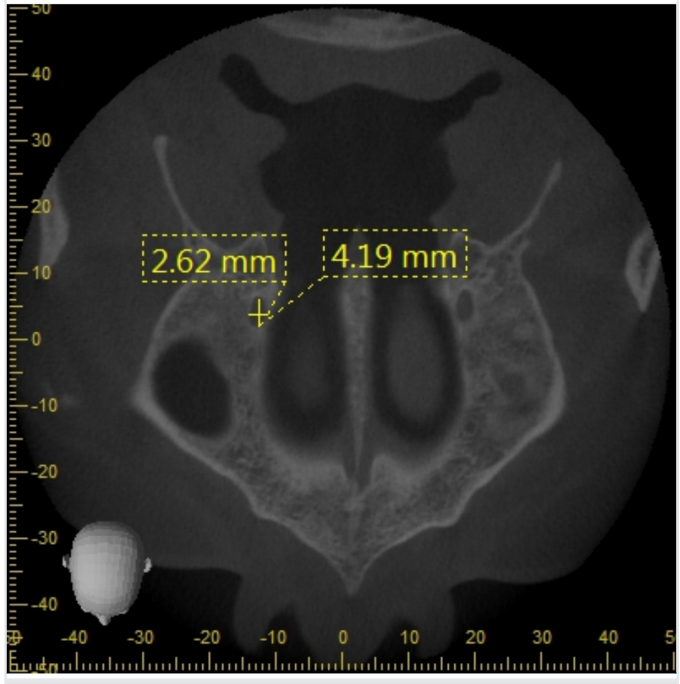

Figure 1. Transverse diameter of right-left FPM in axial sections

FPM: Foramen palatinum majus

minimize individual variability. In this study, descriptive statistics (mean, standard deviation) were calculated for all parameters. Before performing descriptive and quantitative analysis for morphometric measurements and morphological evaluations, it was checked whether the data were normally distributed. Kolmogorov-Smirnov and Shapiro-Wilk tests were used for normality analysis. The means of two independent groups with parameters showing normal distribution were compared with

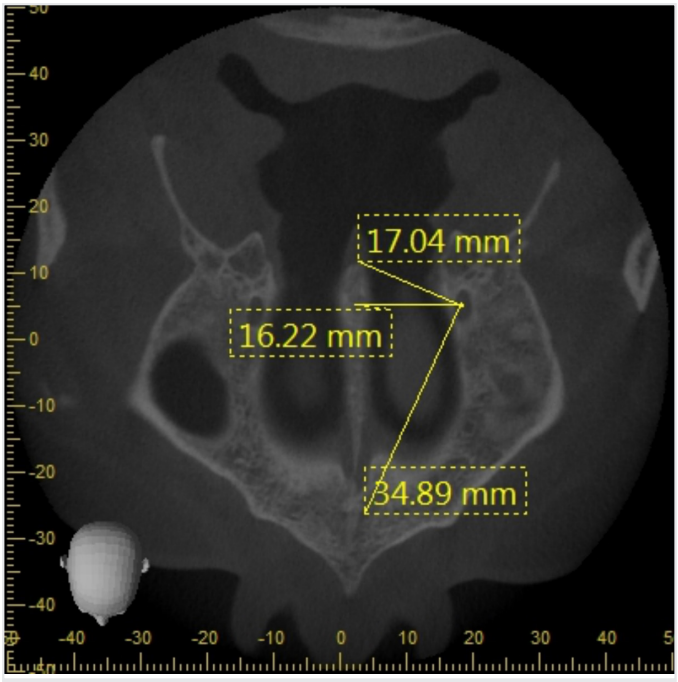

Figure 2. The distance from the center of the Foramen palatinum majus (FPM) to the incisive foramen (FPM-IF), the distance from the center of the FPM to the posterior nasal spine (FPM-PNS), the distance of the center of the FPM to the mid-maxillary suture (FPM-MMS)

Figure 3. Round shape of FPM on an axial CBCT slice

FPM: Foramen palatinum majus, CBCT: Cone-beam computed tomography

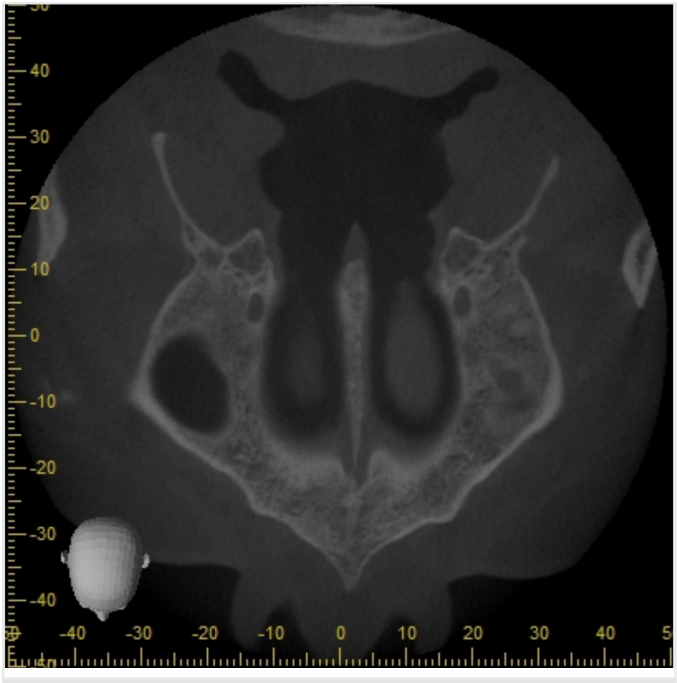

Figure 4. Ovoid shape of FPM on an axial CBCT slice

FPM: Foramen palatinum majus, CBCT: Cone-beam computed tomography

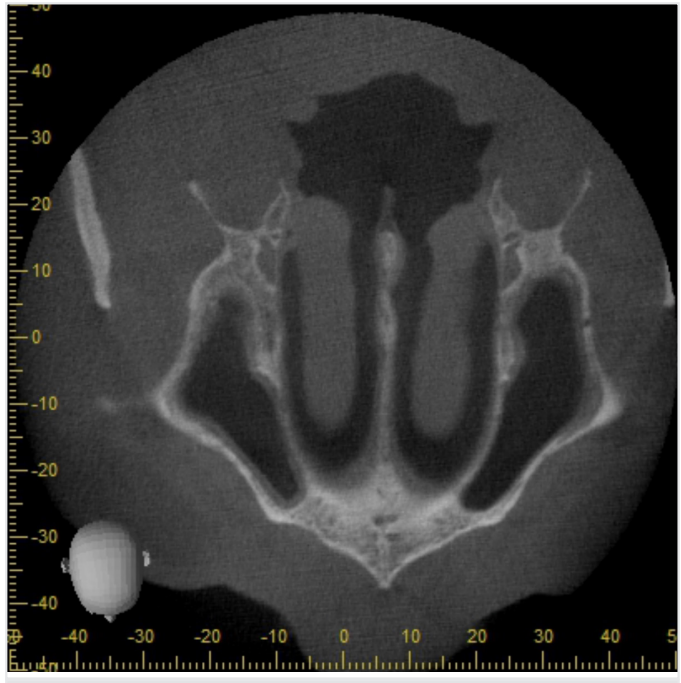

Figure 5. Slit shape of FPM on an axial CBCT slice

FPM: Foramen palatinum majus, CBCT: Cone-beam computed tomography

the independent t-test. The mean of two independent groups with the parameters that did not show normal distribution was compared with the Mann-Whitney U test. The chi-square test was used to determine the relationships between categorical variables and was considered significant at the $p<0.05$ level.

Power analysis

To find significant difference between female and male individuals in terms of left vertical diameter with large effect size (cohen d=1.0) (5), minimum required sample size was calculated as 22 for each group (α=0.05, 1-β=0.90). G-power version 3.1.9 was used for sample size calculation.

Results

In this study, 250 individuals (122 female and 128 male) aged between 18 and 86 were examined. In addition, 125 of the 250 individuals in the study were dentate and 125 were edentulous individuals.

The mean vertical diameter and transverse diameter of FPM were found 4.62±1.33 mm and 1.72±0.56 mm in female dentate individuals. In female edentulous individuals, these values were determined as 5.06±1.70 mm and 2.21±0.7 mm, respectively. The mean distance between FPM and MMS, IF and PNS were 15.82±2.35 mm, 35.8±3.53 mm, and 16.68±1.32 mm in female dentate individuals, respectively. In female edentulous individuals, these values were determined as 16.30±2.37 mm, 36.16±3.58 mm, and 16.91±1.36 mm, respectively.

The mean vertical diameter and transverse diameter of FPM were found 5.33±1.46 mm and 2.28±0.7 mm in male dentate individuals. In male edentulous individuals, these values were determined as 5.22±1.50 mm and 2.56±0.67 mm, respectively. The mean distance between FPM and MMS, IF and PNS were 16.65±2.28 mm, 36.66±3.60 mm, and 17.57±1.54 mm in male dentate individuals, respectively. In male edentulous individuals, these values were determined as 17.70±3.06 mm, 37.60±4.66 mm, and 18.37±1.40 mm, respectively. In Table 1, right and left measurement values of all parameters in dentate and edentulous male and female individuals are given separately. When the measured parameters were compared between dentate and edentulous female and male individuals, a statistically significant difference was found between the genders. Furthermore, it was determined that the values of these parameters were higher in male individuals than in female individuals ($p<0.05$).

When the measurement values of the individuals according to their dentate and edentulous were examined, there was a statistically significant difference in right vertical diameter, right-left transverse diameter, right-left FPM MMS, right-left

Table 1. Minimum, maximum, mean and standard deviation values of the parameters in dentate and edentulous female and male individuals. Comparison between gender in dentate and edentulous individuals ($p<0.05$)

		Female					Male					
Dentition status	**Parameters**	**n**	**min.**	**max.**	**mean**	**SD**	**n**	**min.**	**max.**	**mean**	**SD**	**p**
Dentate	**Right vertical diameter**	69	1.93	10.71	4.45	1.33	56	2.66	9.07	4.92	1.36	>0.05
	Left vertical diameter	69	2.37	10.98	4.79	1.33	56	3.44	10.33	5.74	1.56	<0.001
	Right transverse diameter	69	0.55	3.18	1.67	0.52	56	0.94	3.31	2.09	0.56	<0.001
	Left transverse diameter	69	0.70	3.49	1.78	0.60	56	1.05	4.63	2.46	0.77	<0.001
	Right FPM MMS	69	12.56	19.54	15.75	1.36	56	13.56	19.71	16.56	1.40	<0.01
	Left FPM MMS	69	12.56	35.60	15.89	3.04	56	13.32	34.73	16.75	2.92	<0.01
	Right FPM IF	69	18.14	43.53	35.69	3.87	56	16.05	46.00	36.92	4.12	<0.05
	Left FPM IF	69	30.23	44.91	35.91	3.17	56	30.09	44.46	36.40	3.02	>0.05
	Right FPM PNS	69	13.50	20.56	16.70	1.33	56	14.31	20.06	17.39	1.39	<0.01
	Left FPM PNS	69	13.14	20.15	16.66	1.32	56	14.83	22.56	17.75	1.68	<0.001
Edentulous	**Right vertical diameter**	53	1.72	10.84	4.75	1.60	72	1.22	9.89	5.11	1.48	<0.05
	Left vertical diameter	53	2.45	9.07	5.00	1.66	72	2.62	11.53	5.33	1.51	>0.05
	Right transverse diameter	53	0.89	4.15	2.12	0.67	72	1.10	3.85	2.46	0.57	<0.01
	Left transverse diameter	53	1.22	5.76	2.31	0.72	72	1.06	5.78	2.67	0.76	<0.01
	Right FPM MMS	53	13.43	19.36	16.32	1.35	72	14.30	20.06	17.24	1.40	<0.001
	Left FPM MMS	53	13.08	35.53	16.29	3.08	72	13.78	38.85	18.16	4.06	<0.001
	Right FPM IF	53	16.05	41.69	35.99	3.95	72	15.35	46.65	37.16	5.57	<0.05
	Left FPM IF	53	28.47	42.24	36.33	3.20	72	32.16	49.29	38.04	3.52	<0.05
	Right FPM PNS	53	14.52	19.80	17.06	1.31	72	15.52	20.90	18.23	1.33	<0.001
	Left FPM PNS	53	13.38	21.02	16.76	1.40	72	15.10	21.66	18.50	1.47	<0.001

n: Number of sample, min: Minimum value, max: Maximum value, mean: Mean value, SD: Standard deviation value, p: Significance value, FPM: Foramen palatinum majus, MMS: Mid-maxillary suture, IF: Incisive foramen, PNS: Posterior nasal spine

FPM PNS, and left FPM IF, and these values were higher in edentulous individuals ($p<0.05$) (Table 2).

When the localization of the FPM according to the molar teeth was examined, it was determined that FPM was frequently localized in the interdental region of M2-M3 molars (n=139, 56%). Following this, it was determined that the FPM were localized relative to the molar teeth in the form of M3 (n=77, 31%), D-M3 (n=27, 10%), and M2 (n=7, 3%), respectively.

Although the shape of FPM was statistically significantly associated with the dentition status ($p<0.05$), It was determined that the shape of FPM did not show a statistically significant difference between genders ($p>0.05$) (Table 3).

The round-shaped of FPM (3.6%) in dentate individuals and slit-shaped FPM (26%) in edentulous individuals were the least common forms of FPM. In our study, the most common form of FPM in both dentate (76.8%) and edentulous (77.6%) individuals were determined as ovoid (Table 4).

Table 2. Minimum. maximum. mean. standard deviation and p values of the parameters in dentate and edentulous individuals ($p<0.05$)

	Dentate individuals					Edentulous individuals					
Parameters	n	min.	max.	mean	SD	n	min.	max.	mean	SD	p
Right vertical diameter	125	1.93	10.71	4.66	1.36	125	1.22	10.84	4.95	1.53	<0.05
Left vertical diameter	125	2.37	10.98	5.22	1.51	125	2.45	11.53	5.18	1.57	>0.05
Right transverse diameter	125	0.55	3.31	1.86	0.58	125	0.89	4.15	2.31	0.63	<0.001
Left transverse diameter	125	0.70	4.63	2.08	0.76	125	1.06	5.78	2.51	0.75	<0.001
Right FPM MMS	125	12.56	19.71	16.11	1.43	125	13.43	20.06	16.85	1.44	<0.001
Left FPM MMS	125	12.56	35.60	16.27	3.00	125	13.08	38.85	17.36	3.77	<0.001
Right FPM IF	125	16.05	46.00	36.24	4.01	125	15.35	46.65	36.66	4.96	>0.05
Left FPM IF	125	30.09	44.91	36.13	3.10	125	28.47	49.29	37.31	3.47	<0.01
Right FPM PNS	125	13.50	20.56	17.01	1.39	125	14.52	20.90	17.73	1.43	<0.001
Left FPM PNS	125	13.14	22.56	17.15	1.58	125	13.38	21.66	17.76	1.67	<0.01

n: Number of sample, min: Minimum value, max: Maximum value, mean: Mean value, SD: Standard deviation value, p: Significance value, FPM: Foramen palatinum majus, MMS: Mid-maxillary suture, IF: Incisive foramen, PNS: Posterior nasal spine

Table 3. The opening shape of FPM according to the gender (%)

		Gender					
		Female		Male			
Parameter	**Shape**	**n**	**%**	**n**	**%**	**p**	**X^2**
Right FPM shape	**Round**	6	4.9%	10	7.8%	>0.05	2.236
	Ovoid	96	78.7%	104	81.3%		
	Slit	20	16.4%	14	10.9%		
Left FPM shape	**Round**	7	5.7%	16	12.5%	>0.05	3.490
	Ovoid	95	77.9%	91	71.1%		
	Slit	20	16.4%	21	16.4%		

n: Number of sample, p: Significance value, X^2: Chi-square value, FPM: Foramen palatinum majus

Table 4. The opening shape of FPM according to the dentition satatus (%)

		Dentition status					
		Dentate		Edentulous			
Parameters	Shape	n	%	n	%	p	X^2
Right FPM shape	**Round**	4	3.2%	12	9.6%	<0.05	6.961
	Ovoid	99	79.2%	101	80.8%		
	Slit	22	17.6%	12	9.6%		
Left FPM shape	**Round**	5	4.0%	18	14.4%	<0.01	11.470
	Ovoid	93	74.4%	93	74.4%		
	Slit	27	21.6%	14	11.2%		

n: Number of sample, p: Significance value, X^2: Chi-square value, FPM: Foramen palatinum majus

Discussion

A subepithelial connective tissue graft is the ideal soft tissue graft in the treatment of gingival recessions and its use is increasing day by day. Since the great palatine artery and nerve are located in the palatal donor area, surgeons should work carefully in this area to prevent hemorrhage and paresthesia (7). In addition, it is important to determine the location of the FPM in nerve block anesthesia before palatal surgical procedures. The anesthesia block of the greater palatine is recommended for surgical procedures in the upper molars, maxillary sinus, and nose area (8). The location of FPM in different populations has been investigated in the literature to date, and it has been reported that it may be affected by gender and racial differences (6). However, there is insufficient data on the localization of FPM in edentulous and edentulous individuals. Therefore, in this study, it was aimed to determine the possible variations of FPM and to make a morphometric comparison of FPM using CBCT in dentate and edentulous individuals.

Although FPM has been mostly studied on dry skulls (3,4) in the researches carried out to date, there are also studies conducted with medical CT (9,10) and CBCT (1,5,11-13). CBCT, which provides three-dimensional evaluation with high image quality in addition to low radiation dose, shorter image acquisition time, low cost and easy access compared to medical CT, has become a popular imaging method in maxillofacial region examinations (7,11,14).

Considering it as a guide in determining the FPM position of teeth for dentate individuals, it was determined in this study that FPM was frequently localized at the level of M2-M3 molars (n=139, 56%). Following this, it was determined that the FPM was positioned relative to the molar teeth as M3 (n=77, 31%), D-M3 (n=27, 10%), and M2 (n=7, 3%), respectively. Since there was no such guide in edentulous individuals, according to our results, FPM was located 16.85 on the right and 17.36 mm on the left from the MMS ($p<0.01$), 37.31 mm on the left from the IF ($p<0.01$), and 17.73 mm on the right ($p<0.001$) and 17.76 mm on the left from the PNS ($p<0.01$). These measurement values seem to be higher in edentulous individuals than in dentate individuals. Median maxillary suture and posterior nasal spina are the most important landmarks for locating FPM in edentulous individuals (6). The fact that the parameters measured in edentulous individuals are higher than those in dentate individuals may be related to alveolar bone resorption that occurs with tooth loss (12). In the human cadaver study conducted by Miwa et al. (13) it was stated that the great palatine artery and nerve showed different patterns in edentulous and dentate individuals. When females and males were compared, the measurement values in males were found to be higher. It can be thought that the skull size in males causes this situation (6). When the FPM diameters of the dentate and edentulous individuals were compared, diameter values were found to be higher in edentulous individuals. The mean right vertical diameter of the edentulous individuals was 4.95 mm ($p<0.05$), the right transverse diameter was 2.31 mm ($p<0.001$) and the left transverse diameter was 2.51 mm ($p<0.001$). The larger diameter values in edentulous individuals may be related to the fact that these individuals are older and that the foramen can be seen more easily in osteoporotic boneswith advancing age.

In a meta-analysis by Tomaszewska et al. (6) which included 27 studies, it was reported that FPM was most frequently located at the M3 level with a rate of 63.9%. It has been stated that racial and genetic differences are effective on the change of FPM position. In addition, the application of different methodologies for the measurements seems to be effective on the results (6).

The morphological character of FPM is important as it is the area where the anesthetic solution will be discharged in the anesthetic procedures to be applied, and its different variations may limit the positioning of the injector (15). In our study, the most common form of FPM in all individuals was determined as ovoid. Similarly, in the study conducted by Rapado-González et al. (16) with 110 CBCT images and Lopes et al. (17) on 94 dry skulls, the dominant FPM shape was found to be ovoid.

In a recent study conducted by Lacerda-Santos et al. (18), 60 patients were separated according to three different skeletal face types [brachyfacial (low-angle), dolichofacial (high-angle) and mesofacial (average)], and the position of FPM in different face types was investigated. Although the morphology of FPM is similar in different face types, it has been determined that the FPM is located more distant from the alveolar crest in individuals with dolichofacial face type. Since it can change according to craniofacial development, masticatory system, muscle activity, occlusion, and genetic facial type (18), it should be considered that FPM may have an effect on its position.

Conclusion

Measurements of FPM differ significantly in dentate and edentulous individuals and between male and female genders. FPM is often ovoid and located in the interdental region of M2-M3 molars in toothed patients. Care should be taken in surgical procedures to be performed in this area.

Ethics

Ethics Committee Approval: The study protocol was approved by the Faculty of Dentistry Non-Pharmaceutical and Medical Device Research Ethics Committee (no: 09-79, date: 06.09.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.T., Design: M.T., Data Collection or Processing: D.A., Analysis or Interpretation: M.T., D.A., A.D.A.K., Literature Search: M.T., A.D.A.K., Writing: M.T., A.D.A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Fonseka MCN, Hettiarachchi P, Jayasinghe RM, Jayasinghe RD, Nanayakkara CD. A cone-beam computed tomographic analysis of the greater palatine foramen in a cohort of Sri Lankans. J Oral Biol Craniofac Res 2019;9:306-10.
2. Bahşi İ, Orhan M, Kervancıoğlu P, Yalçın ED. Morphometric evaluation and clinical implications of the greater palatine foramen, greater palatine canal and pterygopalatine fossa on CBCT images and review of literature. Surg Radiol Anat 2019;41:551-67.
3. Wang T-M, Kuo K-J, Shih C, Ho L-L, Liu J-C. Assessment of the relative locations of the greater palatine foramen in adult Chinese skulls. Acta Anat (Basel) 1988;132:182-6.
4. Methathrathip D, Apinhasmit W, Chompoopong S, Lertsirithong A, Ariyawatkul T, Sangvichien S. Anatomy of greater palatine foramen and canal and pterygopalatine fossa in Thais: considerations for maxillary nerve block. Surg Radiol Anat 2005;27:511-6.
5. Aoun G, Nasseh I, Sokhn S, Saadeh M. Analysis of the greater palatine foramen in a Lebanese population using cone-beam computed tomography technology. J Int Soc Prev Commun Dent 2015;5:S82-8.
6. Tomaszewska IM, Tomaszewski KA, Kmiotek EK, Pena IZ, Urbanik A, Nowakowski M, et al. Anatomical landmarks for the localization of the greater palatine foramen – a study of 1200 head CTs, 150 dry skulls, systematic review of literature and meta-analysis. J Anat 2014;225:419-35.
7. Safavi MS, Tehranchi M, Shahab S, Mahdipour Ganji S, Taleghani F. CBCT Evaluation of the Position of Palatal Neurovascular Bundle and the Greater Palatine Foramen in an Iranian Population. Journal of Iranian Dental Association 2021;33:44-50.
8. Kang S-H, Byun I-Y, Kim J-H, Park H-K, Kim M-K. Three-Dimensional Analysis of Maxillary Anatomic Landmarks for Greater Palatine Nerve Block Anesthesia. J Craniofac Surg 2012;23:e199-202.
9. Chundru NSV, Amudala R, Thankappan P, Nagaraju CD. Adenoid cystic carcinoma of palate: A case report and review of literature. Dent Res J (Isfahan) 2013;10:274-8.
10. Kang SH, Byun IY, Kim JH, Park HK, Kim MK. Three-dimensional analysis of maxillary anatomic landmarks for greater palatine nerve block anesthesia. J Craniofac Surg 2012;23:e199-202.
11. Hwang SH, Seo JH, Joo YH, Kim BG, Cho JH, Kang JM. An anatomic study using three-dimensional reconstruction for pterygopalatine fossa infiltration via the greater palatine canal. Clin Anat 2011;24:576-82.
12. Abdullah WH, Alhussaini AHA. The Role of Cone Beam Computed Tomography in Determination of the Greater Palatine Foramen Position Among Iraqi Population. Journal of Baghdad College of Dentistry 2018;30:53-7.
13. Miwa Y, Asaumi R, Kawai T, Maeda Y, Sato I. Morphological observation and CBCT of the bony canal structure of the groove and the location of blood vessels and nerves in the palatine of elderly human cadavers. Surg Radiol Anat 2018;40:199-206.
14. Ikuta CR, Cardoso CL, Ferreira-Júnior O, Lauris JR, Souza PH, Rubira-Bullen IR. Position of the greater palatine foramen: an anatomical study through cone beam computed tomography images. Surg Radiol Anat 2013;35:837-42.
15. Horner K, Jacobs R, Schulze R. Dental CBCT equipment and performance issues. Radiat Prot Dosimetry 2013;153:212-8.
16. Rapado-González O, Suárez-Quintanilla JA, Suárez-Cunqueiro MM. Anatomical variations of the greater palatine canal in cone-beam computed tomography. Surg Radiol Anat 2017;39:717-23.
17. Lopes PTC, Santos AMPV, Pereira GAM, Oliveira VCBD. Morphometric Analysis of the Greater Palatine Foramen in Dry Southern Brazilian Adult Skulls. Int J Morphol 2011;29:420-3.
18. Lacerda-Santos JT, Granja GL, de Freitas GB, Manhães LRC, Jr., de Melo DP, Dos Santos JA. The influence of facial types on the morphology and location of the greater palatine foramen: a CBCT study. Oral Radiol 2022;38:337-43.

Original Article

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Is Ileostomy an Obligation Following Rectal Resection? The Role of Rectal Tube Instead of Ileostomy

Rektal Rezeksiyon Sonrası İleostomi Zorunlu mudur? İleostomi Yerine Rektal Tüpün Rolü

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ABSTRACT

Objective: In laparoscopic distal colon surgery, diverting ileostomy is often used to improve the anastomosis leakage and eliminate the need for secondary surgery. However, complications related to the stoma and its closure have led to new searches. The rectal tube has started to be used as another method to reduce the anastomosis leakage by reducing intestinal pressure and providing drainage. In this study, we aimed to compare the effect of the rectal tube and diverting ileostomy on the outcomes of patients who underwent laparoscopic pelvic subperitoneal surgery.

Methods: Retrospective information was obtained from 66 patients who underwent laparoscopic pelvic subperitoneal surgery in our clinic between 2013 and 2019. The patients were evaluated in two groups: ileostomy and rectal tube. Demographic data, operation findings, pathological results, and follow-up information were evaluated.

Results: Fourty-one of 66 patients who underwent colorectal pelvic peritoneal surgery were in the rectal tube group and 25 were in the ileostomy group. The majority of the patients in the ileostomy group were males (22-88% vs 23-56%, p=0.007); however, there was no difference between the two groups in terms of age, body mass index, comorbidity, and the previous abdominal operation. In the rectal tube group, the number of patients who were diagnosed as having rectal tumors and consequently underwent low anterior resection was higher. In the ileostomy group, the operation time was longer (476±130 vs. 341±114 mins, p=0.0001) and amount of peroperative bleeding was higher (261±260 vs 128±98 mL, p=0.02).

ÖZ

Amaç: Laparoksopik distal kolon cerrahisinde, sıklıkla saptırıcı ileostomi kullanılmaktadır. Bununla beraber rektal tüp intestinal basıncı azaltarak ve drenajı sağlayarak anastomoz kaçağını azaltacak diğer bir yöntem olarak kullanıma girmiştir. Bu çalışmada amacımız laparoskopik distal kolon cerrahisi uyguladığımız hastalarda, rektal tüp ve saptırıcı ileostominin hasta sonuçlarına etkisini karşılaştırmaktır.

Yöntemler: Kliniğimizde 2013-2019 yılları arası laparoskopik distal kolon cerrahisi yapılmış 66 hasta; ileostomi ve rektal tüp olmak üzere iki grupta değerlendirildi. Demografik veriler, operasyon bulguları, patolojik sonuçlar ve takip bilgileri değerlendirildi.

Bulgular: Kırk bir hasta rektal tüp grubunda, 25 hasta ise ileostomi grubunda idi. Rektal tüp grubunda rektal tümör tanılı ve buna bağlı olarak da low anterior rezeksiyon yapılan hastalar daha fazla idi. İleostomi grubunda operasyon süresi daha uzundu (476±130 vs. 341±114 dk, p=0,0001) ve peroperatif kanama miktarı daha fazla idi (261±260 vs 128±98 mL, p=0,02). Postoperatif ikinci günkü ağrı skalası rektal tüp grubunda daha düşük idi (2,8±1,5 vs. 4,7±2,9, p=0,008). Bir ve üçüncü günlerdeki ağrı skalası puanları ise rektal tüp grubunda daha düşük olmasına rağmen, istatistiksel olarak iki grup arasında anlamlı fark yoktu. Hastaların kozmetik skorları rektal tüp grubunda daha iyiydi (9,3±0,9 vs 7,2±1,9, p=0,001).

Sonuç: Laparoksopik pelvik periton altı kolorektal cerrahide; rektal tüpün ileostomiye göre sonuçlarının daha kötü olmadığı, uygun olgularda tercih edilebileceği ve stoma ilişkili sorunları azaltabileceği gözlenmiştir.

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Intraoperative and postoperative complications of the patients were similar in both groups. The pain scale on the postoperative second day was lower in the rectal tube group (2.8±1.5 vs. 4.7±2.9, p=0.008). Although the pain scales on day 1 and day 3 were lower in the rectal tube group, there was no statistically significant difference between the two groups. The oncological results were similar during the average follow-up period of 28.3±18.5 months. The cosmetic scores of the patients were better in the rectal tube group (9.3±0.9 vs. 7.2±1.9, p=0.001).

Conclusion: In laparoscopic pelvic subperitoneal colorectal surgeries; it has been observed that the results of the rectal tube are not worse than ileostomy, it can be preferred in appropriate cases and reduce stoma-related problems.

Keywords: Minimally invasive surgery, colon cancer, laparoscopy, low anterior, loop, diverting

Anahtar Sözcükler: Minimal invaziv cerrahi, laparoskopik kolorektal, laparoskopi, low anterior, loop, saptırıcı

Introduction

Anastomosis leakage is one of the most important causes of mortality and morbidity in reconstructive distal colon surgery. In patients with anastomosis leakage without peritonitis; conservative treatment is preferred by cleaning and draining the fistula cavity (1). Therefore, many methods have been tried, especially diverting ileostomy, to reduce the leakage by providing drainage. The complications of diverting ileostomy and the closure-related complications have led to the search for different methods to perform the drainage process. The rectal tube application (2), which has functions such as drainage, reduction of endoluminal pressure, and promotion of gastrointestinal motility, has found its use in this field with the fact that it does not require additional surgery.

This study aims to investigate the effect of ileostomy and rectal tube use on the outcomes of the patients undergoing laparoscopic pelvic subperitoneal surgery.

Methods

This study was approved by İnönü University Ethical Committee (2019/447). Sixty-six patients who underwent laparoscopic low anterior resection and total proctocolectomy in our clinic between March 2013 and July 2019 were included in the study. After the patients were given detailed information, they were asked about their operation preferences and a detailed consent form was obtained from them. Forty-one patients who underwent rectal tubes and 25 patients who underwent a diverting ileostomy were analyzed in two groups. The selection of specimen extraction was made according to patient preference and technical compliance. After the operation was completed, the rectal tube (28 mm Petzer's tube) was placed proximal to anastomosis as controlled by laparoscopic image (3). The patients' age, gender, body mass index (BMI), additional disease, operation history, ASA scores, operation time, amount of bleeding, incision size, peroperative and postoperative complications, hospitalization time, piece pathology, tumor size, the number of removed lymph nodes, the number of positive lymph nodes, tumor stage, visual analog scale (VAS) score, cosmetic score, long-term complication, presence of relapse and general survival parameters were examined. Complications of the patients undergoing diverting ileostomy and their perioperative findings during the closure were searched. The largest size specified in pathological reports was taken as the tumor size. The VAS scores of patients were examined with 10 being the highest pain score, and 1 being the lowest before they received any analgesic support in the first three postoperative days. The cosmetic status was scored as 10 being the best score and 1 being the worst. Patients were called by phone during the follow-up process and information about their recent status, hernia, and the cosmetic score was obtained. Statistical analyses were made for all the data and reported in means and percentages. Continuous variables were analyzed by unpaired t-test or Mann-Whitney U test. Categorical variables were analyzed with chi-square Test and Fisher-Exact Test. A p-value of <0.05 was accepted statistically significant. The data were analyzed using SPSS version 16.0 and Microsoft Excel 2013.

Results

Fourty-five (68%) of the patients included in the study were males and the mean age was 56.1±13.4. The average BMI was 26.5±3.9 and 29 (44%) of the patients had comorbidity. Thirteen of the patients (19%) had a history of pre-existing abdominal surgery. Fourty-six of the patients (69%) had rectal cancer, 13 (19%) had familial adenomatosis polyposis and 7 (10%) had rectal cancer and liver metastasis (Table 1).

Of a total of 66 laparoscopic surgical procedures; 46 (69%) were low anterior resection, 13 (19%) were total proctocolectomy and pouch-anal anastomosis, 5 (7%) were low anterior resection and liver metastasectomy and 2 (3%) were low anterior resection and major hepatectomy. The J-pouch anal anastomosis was performed in 11 of the patients who underwent pouch-anal anastomosis and W-pouch anal anastomosis was performed in 2. One of the patients who underwent major hepatectomy was in the rectal tube group and underwent left hepatectomy, the other was in the ileostomy group and underwent right hepatectomy.

The mean duration of the operation was 386±132 mins, and the mean amount of intraoperative bleeding was 182±193 mL. Piece extraction was performed through the natural hole in 36 (54%) patients, and through a suprapubic incision in 30 (46%) patients. The transanal pathway was used in 32 (88%) patients in the group undergoing NOSE surgery, while the transvaginal pathway was used in 4 (12%) patients; and peroperative complications were observed in 8 patients. Five of these patients had internal abdominal bleeding. The bleeding area was in the sacral venous plexus in 2 patients and the bleeding was stopped with a tampon. One patient had bleeding while the splenic flexure was being lowered, which was stopped with cautery. The other 2 patients underwent major hepatectomy and the bleeding from liver parenchyma was stopped with the help of a ligature (Medtronic-5 mm). One patient had fecal transmission and was cleared while transvaginal extraction was performed. After anastomosis was performed in 2 patients, the air leakage test was found to be positive and support sutures were placed in these areas. The operation was terminated when the control air test showed no leaks. When the two groups were compared; no difference was detected in terms of the operation time, blood loss, intra-, and post-operative complications. Intra- and extra-abdominal complications were similar. Although the VAS scores in the early postoperative period were found to be low in the rectal tube group, a significant difference in VAS values was determined only on the first day (p=0.008) (Table 2).

Anastomosis leakage was observed in 3 patients in both groups. One patient in each of the two groups required postoperative reoperation. These patients underwent end colostomy and drainage. One patient in each of the two groups underwent percutaneous drainage due to intra-abdominal abscess. Three of the patients in the rectal tube group underwent dilatation in the late period due to anal stenosis. Two of the patients in the ileostomy group underwent late-stage anal dilatation due to anal stenosis and 1 of these patients underwent pull-through since the dilatation procedure was not successful.

Table 1. Preoperative parameters

Parameters	Rectal tube (n=41)	Ileostomy (n=25)	P
Gender (female/male)	18/23	3/22	0.007
Age			
Mean SD	57.3±13.8	54.2±12.6	0.36
Median (range)	60 (30-79)	56 (25-82)	
BMI			
Mean SD	26.6±4.0 kg/m^2	26.3±3.7 kg/m^2	0.76
Median (range)	25.6 (18.4-34.1)	26.7(20.1-32.9)	
ASA			
Mean SD	2.0±0.6	1.9±0.6	0.51
Median (range)	2 (1-3)	2 (1-3)	
Patients with co-morbidity	18 (44%)	11 (44%)	1.00
Diabetes mellitus	10 (24%)	5 (20%)	
Hypertension	13 (31%)	6 (24%)	
Chronic obstructive pulmonary disease	3 (7%)	1 (4%)	
Cardiac disease	1 (2%)	0 (0%)	
Chronic kidney disease	2 (4%)	0 (0%)	
Periferic vascular disease	5 (12%)	3 (12%)	
Patients with prior abdominal surgery	8 (19%)	5 (20%)	1.00
Gynecologic operation	4	1	
Open inguinal hernia repair	2	1	
Opening ileostomy	0	1	
Subtotal gastrectomy	0	1	
Open appendectomy	4	0	
Laparoscopic cholecystectomy	1	1	
Disease			
FAP	5 (12%)	8 (32%)	0.06
Rectal tumor	33 (80%)	13 (52%)	0.02
Rectal tumor + liver metastases	3 (7%)	4 (16%)	0.41
Neoadjuvant radiotherapy	12 (29%)	13 (52)	0.07

BMI: Body mass index, SD: Standart deviation, FAP:

Table 2. Intraoperative and postoperative outcomes

Parameters	Rectal tube (n=41)	Ileostomy (n=25)	P
Operation type			
LAR	33	13	0.02
LAR + liver metastasectomy	2	3	0.35
LAR + major hepatectomy	1	1	1.00
Total colectomy (J/W pouch)	5 (5/0)	8 (6/2)	0.06
Extraction type			
NOSE (TA/TV)	27 (23/4)	9 (9/0)	0.02
Suprapubic	14	16	
Duration of surgery			
Mean SD	341±114 minutes	476±130 minutes	0.0001
Median (range)	360 (180-600)	450 (240-720)	
Intraoperative bleeding			
Mean SD	128±98 mL	261±260 mL	0.02
Median (range)	100 (10-400)	200 (20-1000)	
Incision length			
Mean SD	7.4±2.0 cm	7.3±1.9 cm	0.90
Median (range)	6.7 (5-12)	7 (5-12)	
Intraoperative complications	4 (9%)	4 (16%)	0.46
Fecal contamination	0	1	
Bleeding	3	2	
Air leak test (+)	1	1	
Postoperative complications	16 (39%)	13 (52%)	0.32
Intraabdominal complications			
Bleeding	1	1	
Abscess#	2	2	
Anastomotic leakage#	3	3	
Anastomotic stenosis	3	2	
Rectovaginal fistula	3	1	
Ileostomy invagination	0	1	
Paralytic ileus	3	2	
Biliary fistula	0	1	
Extraabdominal complications			
Atelectasis	1	1	
Pleural effusion	0	1	
Urinary infection	2	0	
VAS score (total)			
Mean SD	3.1±2.0	4.0±2.9	0.15
Median (range)	3 (0-9)	4 (0-10)	
VAS score on day 1			
Mean SD	4.4±2.3	4.8±3.2	0.55
Median (range)	4 (2-9)	5 (1-10)	
VAS score on day 2			
Mean SD	2.8±1.5	4.7±2.9	0.008
Median (range)	3 (0-6)	5 (1-10)	
VAS score on day 3			
Mean SD	2.1±1.1	2.5±2.0	0.29
Median (range)	2 (0-4)	2 (0-7)	

Table 2. Continued

Parameters	Rectal tube (n=41)	Ileostomy (n=25)	P
Length of hospital stay			
Mean SD	9.5±7.2 days	12.6±9.4 days	0.13
Median (range)	7 (4-43)	9 (3-42)	
Cosmetic score			
Mean SD	9.3±0.9	7.2±1.9	0.001
Median (range)	10 (7-10)	7 (4-10)	
Recurrence^	3 (9%)	5 (23%)	0.23
Duration of follow-up			
Mean SD	30.0±12.0 months	25.7±22.2 months	0.31
Median (range)	15 (1.5-79)	18 (3-78)	
Stoma-free life	39/41 (95%)	20/25 (80%)	0.09

TA: Transanal, TV: Transvaginal, #Anastomotic leakage and abdominal abscess in the same two patients in both groups, SD: Standart deviation
^Statistics were made among patients with tumor

Table 3. Pathology of the malignancies

Parameters	Rectal tube (n=33)	Ileostomy (n=21)	P
T			
T1	2	0	0.51
T2	3	3	0.66
T3	22	15	0.77
T4 (a-b)	6 (6-0)	3 (3-0)	0.72
N			
0	20	8	0.08
1 (a-b-c)	6 (4-1-1)	8 (6-2-0)	0.12
2 (a-b)	7 (0-7)	5 (2-3)	1.00
M			
0	27	15	0.50
1 (a-b)	6 (5-1)	6 (6-0)	0.50
Stage			
1	4	2	1.00
2 (a-b-c)	13 (12-1-0)	5 (4-1-0)	0.37
3 (a-b-c)	10 (1-4-5)	8 (1-4-3)	0.56
4 (a-b)	6 (5-1)	6 (6-0)	0.50
Tumor size			
Mean SD	4.3±1.7	4.2±2.0	0.84
Median (range)	3.8 (1.5-8.5)	4 (1-9)	
Removed lymph node (total)			
Mean SD	25.9±22.5	25.1±16.5	0.88
Median (range)	20 (3-125)	23 (0-59)	
Positive lymph node			
Mean SD	4.0±9.5	2.8±5.1	0.59
Median (range)	0 (0-42)	1 (0-23)	

SD: Standard deviation

In 4 patients in the ileostomy group (16%), stoma-related complications were detected. The parastomal hernia was detected in 2 of them and the stoma was repaired during closure. One patient had dehydration and acute renal failure, and the stoma was closed in the early period. One patient had stoma prolapse and underwent revision surgery. One patient (4%) had pleural effusion and wound infection due to stoma closure. This patient recovered with medical treatment without the need for intervention. In 2 patients (8%), the stoma could not be closed. One of them underwent colon resection with right hepatectomy and died in the postoperative 3rd month. The other underwent low anterior resection and liver metastasectomy in the post-operative 3rd month, and died in the 7th month.

When pathology results were examined, it was found that 54 (81%) of patients had malign tumors. Fifty-three (98%) of the tumors were adenocarcinomatous tumors and one was a neuroendocrine tumor. Preoperative polypectomy pathology was invasive adenocarcinomatous tumor in 3 patients, while the invasive focus was not detected in the resection material. Pathologies of the patients with benign tumors were reported as adenoma with dysplasia in 6 patients and adenomatosis polyposis in 3 patients. Tumor size was 4.2±1.9 cm on average. The mean number of lymph nodes removed was 25.6.2±20.4, while the number of positive lymph nodes was 3.5±8.1. When tumor stages were examined, it was found that 12 (22%) were stage 4, 18 (33%) were stage 3, 18 (33%) were stage 2 and 6 (11%) were stage 1. The pathology results of the two groups are given in Table 3, comparatively.

While no mortality was seen in any patient in the early postoperative period, the total rate of mortality was 16%. The mean follow-up period of the patients was 28.3±18.5 months. The recurrence rate of our patients was 14% when evaluated specifically in patients with tumor. Two (3%) of the patients with recurrence had liver metastasis, 1 (1%) had lung metastasis and the other 5 (9%) had an intra-abdominal recurrence.

Discussion

Anastomosis leakage is one of the most important complications affecting postoperative morbidity and mortality in low anterior resection surgery. The mechanism of anastomosis leakage has not yet been fully understood, but intraluminal pressure is known to play an active role in this (4). Ileostomy is among the most commonly used methods for reducing this pressure and diverting fecal content. Studies have shown that ileostomy reduces anastomosis leakage clinic (fecal peritonitis, sepsis), but does not change the leakage rates (5). However, the increase in morbidity caused by ileostomy itself or closure surgery creates hesitations in practice. Interventions such as pelvic drainage, cannula ileostomy, supportive sutures, and fibrin glue have also been reported to reduce anastomosis leakage (6-9). However, insignificant and conflicting results have led to a lack of consensus on this issue. Another of these techniques is the rectal tube (10). Reduction of intraluminal pressure and lack of necessity for additional surgery have led researchers to investigate the applicability of this method. Thanks to this method, which has been in use in our clinic since 2013, patients are saved from additional incisions and a life with a stoma. However, we have conflicting data on whether it is as effective as ileostomy, which is the main reason that has led us to this study.

Anastomosis leakage is seen at rates above 15% (11). It is known that this frequently-seen complication causes morbidity by 20-30% and mortality by 7-12%. It also increases local recurrence reducing long-term survival (12). For this reason, it is very important to control this complication as much as possible before it worsens the clinic picture and re-operation is needed. While our study did not find a difference between the two groups in terms of anastomosis leakage, the requirement for reoperation in these patients was found to be similar. Studies comparing the two groups similarly found no difference in the need for reoperation between the rectal tube and ileostomy (12). In addition, it has been seen that the need for reoperation in patients who do not use any drainage methods is quite minimized with the rectal tube (82%-28%) (2).

In addition to the ileostomy surgical procedure, it is known that it has the disadvantages of more bleeding and longer operation time. Some studies show that higher amount of bleeding during the operation and longer duration of the operation increase the risk of anastomosis leakage. On the other hand, other studies show opposite results that it is not related to anastomosis leakage (13,14). Studies comparing ileostomy and rectal tube show that ileostomy prolongs the duration of operation and increases the amount of peroperative bleeding (10,11). Our study, similarly, showed that the duration of operation was shorter and the amount of bleeding was lower in the rectal tube group. Besides, some of the stomas opened cannot be closed and the exposure to complications increases. The non-closure rate, which was determined as 8% in our study, was stated as 6% in the literature (12).

Ileostomy may lead to many complications such as wound infection, prolapse, retraction, stenosis, necrosis, parastomal hernia, and ileus. Therefore, the risk factors of anastomosis leakage for selective use of ileostomy and the method to be used in place of this technique have been frequently investigated. In our study, the total complication rate due to ileostomy was determined as 20%. This rate is similarly given as 19% in the literature. However, complications related to stoma closure are not added to this ratio (15).

With the improvements in minimally invasive surgery; postoperative pain scores and cosmetic scores have become the most important markers affecting patient satisfaction. Although the VAS scores in the rectal tube group in our study were lower, it was seen that this difference became significant in the day 2 scores. In addition, cosmetic scores were found to be higher in the rectal tube group. The rectal tube vs ileostomy study on patients receiving neoadjuvant similarly found that the cosmetic score was lower in the rectal tube group (10). In this group of patients with high morbidity, it is clear that these criteria, which contribute to a comfortable postoperative process, are important.

Conclusion

No drawbacks were found for rectal tubes to reduce the anastomosis leakage and the need for reoperation in laparoscopic pelvic subperitoneal surgery. Besides, rectal tubes increased postoperative patient comfort significantly and, even if not significant, increased the likelihood of stoma-free life proportionally. We think that it can be considered instead of diverting stoma in suitable patients.

Ethics

Ethics Committee Approval: This study was approved by İnönü University Ethical Committee (2019/447).

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: E.G., Concept: C.K., Design: E.G., C.K., Data Collection or Processing: E.G., F.S., Analysis or Interpretation: E.G., C.K., Literature Search: E.G., F.S., Writing: E.G.

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References

1. Peng J, Lu J, Xu Y, Guan Z, Wang M, Cai G, et al. Standardized pelvic drainage of anastomotic leaks following anterior resection without diversional stomas. Am J Surg 2010;199:753-8.
2. Xiao L, Zhang WB, Jiang PC, Bu XF, Yan Q, Li H, et al. Can transanal tube placement after anterior resection for rectal carcinoma reduce anastomotic leakage rate? A single-institution prospective randomized study. World J Surg 2011;35:1367-77.
3. Kayaalp C, Yagci MA, Soyer V. Laparoscopic and natural orifice transluminal restorative proctocolectomy: no abdominal incision for specimen extraction or ileostomy. Videosurgery Miniinv 2016;11:115-20.

4. Hallbook O, Sjodahl R. Anastomotic leakage and functional outcome after anterior resection of the rectum. Br J Surg 1996;83:60-2.
5. Wong NY, Eu KW. A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study. Dis Colon Rectum 2005;48:2076-9.
6. Huh JW, Kim HR, Kim YJ. Anastomotic leakage after laparoscopic resection of rectal cancer: the impact of fibrin glue. Am J Surg 2010;199:435-41.
7. Peng J, Lu J, Xu Y, et al. Standardized pelvic drainage of anastomotic leaks following anterior resection without diversional stomas. Am J Surg 2010;199:753-8
8. Baek SJ, Kim J, Kwak J, Kim SH. Can trans-anal reinforcing sutures after double stapling in lower anterior resection reduce the need for a temporary diverting ostomy? World J Gastroenterol 2013;19:5309-13.
9. Hua H, Xu J, Chen W, Zhou X, Wang J, Sheng Q, et al. Defunctioning cannula ileostomy after lower anterior resection of rectal cancer. Dis Colon Rectum 2014;57:1267-74.
10. Gundogan E, Kayaalp C. Can rectal tube be used instead of ileostomy in patients undergoing rectal resection after neoadjuvant chemo-radiotherapy?. Ann Med Res 2020;27:38-44.
11. Xiao L, Zhang WB, Jiang PC, Bu XF, Yan Q, Li H, et al. Can transanal tube placement after anterior resection for rectal carcinoma reduce anastomotic leakage rate? A single-institution prospective randomized study. World J Surg 2011;35:1367-77.
12. Kim MK, Won DY, Lee JK, Kang WK, Kim JG, Oh ST. Comparative study between transanal tube and loop ileostomy in low anterior resection for mid rectal cancer: a retrospective single center trial. Ann Surg Treat Res 2015;88:260-8.
13. Telem DA, Chin EH, Nguyen SQ, Divino CM. Risk factors for anastomotic leak following colorectal surgery: a case-control study. Arch Surg 2010;145:371-6.
14. Kawada K, Hasegawa S, Hida K, Hirai K, Okoshi K, Nomura A, et al. Risk factors for anastomotic leakage after laparoscopic low anterior resection with DST anastomosis. Surg Endosc 2014;28:2988-95.
15. Rullier E, Le Toux N, Laurent C, Garrelon JL, Parneix M, Saric J. Loop ileostomy versus loop colostomy for defunctioning low anastomoses during rectal cancer surgery. World J Surg 2001;25:274-7.

Original Article

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Ivermectin Induces Oxidative Stress and DNA Damage in Breast Cancer Cells

İvermektin Meme Kanseri Hücrelerinde Oksidatif Stres ve DNA Hasarı Oluşturuyor

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ABSTRACT

Objective: Breast cancer (BC) remains to be one of the most diagnosed cancer types among women around the world. Drug repurposing is suggested to be a convenient alternative for drug development in cancer treatment. Ivermectin, the antiparasitic agent produced by the bacterium *Streptomyces avermitilis*, is currently being examined thoroughly in oncology and has begun to be seen as a potential drug candidate for BC therapy. However, studies are limited, and the exact anti-tumorigenic mechanism is not yet clarified in breast cancer.

Methods: For elucidating the molecular mechanisms of Ivermectin's potential anticancer effects, we have examined its *in vitro* effects on BC cells in terms of cell viability, intracellular ROS levels, glutathione levels, mitochondrial membrane potential, apoptosis, and DNA damage.

Results: Ivermectin induces apoptosis via oxidative stress and DNA damage in BC cells.

Conclusion: The *in vitro* mechanistic studies of promising anticancer agents for repurposing are essential guides for drug developers. For this purpose, ivermectin should be further studied as a drug candidate for its potential in the treatment of breast cancer.

Keywords: Ivermectin, breast cancer, drug repurposing, DNA damage, oxidative stress

ÖZ

Amaç: Meme kanseri (MK), tüm dünyada kadınlar arasında en sık teşhis edilen kanser türlerinden biri olmaya devam etmektedir. İlaçların yeniden hedeflendirilmesinin (repurposing) kanser tedavisinde ilaç geliştirme için uygun bir alternatif olduğu ileri sürülmektedir. *Streptomyces avermitilis* bakterisi tarafından üretilen anti-paraziter ajan olan İvermektin, şu anda onkolojide kapsamlı bir şekilde incelenmektedir ve MK tedavisi için potansiyel bir ilaç adayı olarak görülmeye başlanmıştır. Bununla birlikte, çalışmalar sınırlıdır ve MK'de kesin anti-tümörijenik mekanizma henüz açıklığa kavuşturulmamıştır.

Yöntemler: İvermektin'in potansiyel antikanser etkilerinin moleküler mekanizmalarını aydınlatmak için MK hücreleri üzerindeki *in vitro* etkilerini hücre canlılığı, hücre içi ROS seviyeleri, glutatyon seviyeleri, mitokondriyal membran potansiyeli, apoptoz ve DNA hasarı açısından inceledik.

Bulgular: İvermektin, MK hücrelerinde oksidatif stres ve DNA hasarı yoluyla apoptozu indükler.

Sonuç: Yeniden hedeflendirmek için umut verici anti-kanser ajanlarının *in vitro* mekanik çalışmaları, ilaç geliştiriciler için temel kılavuzlardır. İvermektin, bu amaçla MK tedavisindeki potansiyeli açısından bir ilaç adayı olarak incelenmeye devam edilmelidir.

Anahtar Sözcükler: İvermektin, meme kanseri, ilaç yeniden hedeflendirilmesi, DNA hasarı, oksidatif stres

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Introduction

Breast cancer (BC) remains to be one of the most diagnosed cancer types among women around the world (1). Prognosis is poor and survival is low in BC, although various treatment recommendations such as local and systemic therapy are offered along with new generation targeted therapies depending on the subtype of the cancer (2-4). BC can be categorized into four subtypes: Luminal A, luminal B, HER2-enriched, and basal-like (4,5). Luminal-like subtypes, which constitute 70% of patients, are hormone receptor-positive (estrogen and/or progesterone) but lack human epidermal growth factor 2 receptor (ERBB2; HER2). The HER2-enriched subtype constitutes 15-20% of patients with BC. And lastly, the basal-like subtype (15%), also called "triple-negative", lacks the receptors of estrogen, progesterone, and HER2 (4).

Drug repurposing is suggested to be a convenient alternative for drug development in cancer treatment (6). In this regard, ivermectin, the antiparasitic agent produced by the bacterium *Streptomyces avermitilis,* which has been used since 1987 (7), is currently being examined thoroughly in oncology and has been found to have *in vitro* antiproliferative/cytotoxic properties against cervical cancer, gastric cancer, ovarian cancer, colon cancer, glioblastoma, leukemia and melanoma (8-15).

Ivermectin has also been tested against different types of BC cell lines and thus began to be seen as a potential drug candidate for BC therapy (16-19). Although ivermectin was reported to block the PAK1/Akt Axis in BC cells and induce autophagy both *in vitro* and *in vivo* (16,17) the exact molecular mechanism of ivermectin's inhibitory effects is not yet clarified. For this reason, ivermectin was selected to be studied for elucidating the molecular mechanisms of its potential anticancer effects. We examined the drug's *in vitro* effects on BC cells in terms of cell viability, intracellular ROS levels, glutathione levels, mitochondrial membrane potential, apoptosis, and DNA damage. The promising effects of ivermectin against cancer cell lines make it suitable for further evaluation, suggesting its potential for taking place as an alternative in the treatment of breast cancer.

Methods

Chemicals

Ivermectin, fetal bovine serum (FBS), Leibovitz's L15 Medium, Eagle's Minimum Essential Medium (EMEM), dimethylsulfoxide (DMSO), 2'7'-dichlorodihydroflorescein-diacetate (H_2DCF-DA), penicillin/streptomycin (P/S), acridine orange (AO), ethidium bromide (EB), and 3,3'-dihexylocarbocyanine iodide [DiOC6 (3)] were purchased from Sigma-Aldrich (Seelze, Germany). The luminometric ATP kit was supplied by Promega (CellTiter-Glo® Luminescent Cell Viability Assay, Madison, USA). Other chemicals and solutions used in the experiments were all used in analytical quality.

Cell Culture

Human BC cell lines MCF7 American Type Culture Collection (ATCC® HTB-22™), MDA MB231 (ATCC® CRM HTB-26™), and healthy human breast epithelial cell line 184A1 (ATCC® CRL8798™), which were used in the experiments, were commercially obtained from the ATCC. MCF7 was cultured and cultivated in complete media containing 10% FBS, 1% P/S, and 0.01 mg/mL in EMEM at 37 °C in incubators containing 5% CO_2. MDA MB231 was cultured and cultivated in complete media containing 10% FBS and 1% P/S, Leibovitz's L15 Medium at 37 °C in incubators containing 5% CO_2. 184A1 was cultured and cultivated in base medium (MEBM), and the MEGM kit included 0.005 mg/mL transferrin and 1 ng/mL cholera toxin at 37 °C in incubators containing 5% CO_2. Cells were seeded $5x10^3$/well to 96 opaque well plates (black or white) for cytotoxicity, intracellular ROS, glutathione, and mitochondrial membrane potential levels. For genotoxicity and apoptosis, $50x10^3$ cells per well were seeded in 6-well plates. All experiments in the study were left for 24 h incubation for the adhesion of the cells, and another 24 h at 37 ˚C to examine the cytotoxic, genotoxic, and apoptotic, and other effects of the administered substances. Before all experiments, the viability of the cells was checked with trypan blue, and the number of cells was counted in the Thoma slide.

Cytotoxicity of Ivermectin

In the study, a luminometric ATP assay was used to analyze cytotoxicity. The commercially purchased CellTiter-Glo® luminescence cell viability kit is a similar method based on the amount of ATP that indicates the presence of living cells. The principle of the method is that the amount of ATP is proportional to the number of cells (20), and in the presence of ATP, luciferin in the cells in the medium emits luminescence by converting to the recombinant luciferase enzyme (21). Ivermectin (2.5-250 µM) prepared at different concentrations was added to $5x10^3$ cells after 24 h in opaque white 96-well plates and incubated for 24 h. After incubation, the ATP solution was added, and luminescence measurement was taken in Thermo Varioskan multiplate reader (Varioskan Flash Multimode Reader, Thermo, Waltham, USA) within 5 minutes. Luminescence spreading in the presence of ATP was reported as relative luminescence units. Cell viability was expressed relative to the control group considered 100% (Figure 1). Half maximum growth inhibitor concentration (IC_{50}) values were calculated from the non-linear regression analysis dose-response curves. All doses were repeated four times.

Generation of Reactive Oxygen Species

Intracellular ROS production was evaluated using the fluorescent signal indicator 2,7-dichlorodihydroflorescein-diacetate (H_2DCF-DA). The colorless H_2DCF-DA is oxidized by intracellular ROS in the medium and converts to a green fluorescent DCF. There is a fluorescence correlation between the increasing amount of ROS and diffusing fluorescence (22). Ivermectin prepared at different concentrations (2.5-250 µM) was added to the cells, which were seeded in 96 opaque black

plates 15x10³ cell/well for 24 h treatment. After 24 h treatment, the media was removed and washed three times with 1xdPBS. 100 µL 10 µM H_2DCF-DA prepared in DMSO was added and incubated at 37˚C for 30 minutes in a CO_2 incubator. The fluorescence intensity of DCF formed after incubation was measured using the Ex: 488nm / Em: 525nm fluorescence plate reader (Varioskan Flash Multimode Reader, Thermo, Waltham, USA). Results were calculated relative to the control group, with 0.1% DMSO compared to ATP (iROS/ATP) (21). All doses were repeated four times.

Intracellular Glutathione Levels

In this study, a luminometric glutathione kit was used to measure intracellular glutathione levels. The commercially purchased GSH-Glo™ Glutathione Assay luminescence glutathione kit reduces glutathione with the glutathione-s transferase enzyme while converting the luciferin-NT substrate in the kit to luciferin. ATP emerges in the environment during this conversion. The luciferase that occurs in the environment transforms into recombinant luciferase enzyme and converts to oxyluciferin, and emits luminescence (23). Ivermectin prepared at different concentrations (2.5-250 µM) was added to 15x10³ cells after 24 h in opaque white 96-well plates and incubated for 24 h. After incubation, the glutathione solution was added, and luminescence measurement was done in Thermo Varioskan multiplate reader within 5 minutes. Results were calculated relative to the control group added with 0.1% DMSO. All doses were repeated four times.

Mitochondrial Membrane Potential

Mitochondrial membrane potential (MMP-$\Delta\psi$m) is an essential parameter of mitochondrial function and an indicator of cellular health and apoptosis. The fall of MMP indicates the loss of mitochondrial membrane integrity, which reflects the initiation of the proapoptotic signal. In this protocol, 3,3'-hexyloxycarbocyanine iodide [DiOC6(3)], which is a cell-permeable, green fluorescence, lipophilic dye, accumulates in mitochondria. After 24 h incubation of ivermectin (2.5-250 µM), the media was removed and washed. Fourty nM DiOC6(3) was added and incubated at 37 °C for 15 minutes, after washing three times with 1xdPBS. Fluorescence intensity was measured using Ex: 484 nm/Em: 501 nm fluorescence plate reader (Varioskan Flash Multimode Reader, Thermo, Waltham, USA). The results were calculated relative to the control group compared to ATP (MMP/ATP) (21,24). All doses were repeated four times.

Apoptosis

AO/EB dye is a double staining method used to evaluate morphological changes in cells (25). The AO is a vital dye which stains both living and dead cells. EB dye only stains cells that have lost membrane integrity. Healthy cells appear to be homogeneous green, and early apoptotic cells contain bright green spots, especially in their nuclei due to chromatin condensation and nuclear breakdown. Late apoptotic cells turn orange because they contain both AO and EB. However, necrotic cells appear to be distorted red since they have a different nuclear morphology and dye density as they contain condensed chromatin as opposed to healthy cells (26). Ivermectin's doses below IC_{50} (2.5-30 µM) were added in 6-well plates. After 24 h incubation, cells were removed with Trypsin-EDTA and washed three times with dPBS. Cells were centrifuged at 500x g for 5 minutes at +4 ˚C, and then the supernatant was discarded. Ten µL of cell pellet and 10 µL of AO/EB solution (100 µg/mL AO +100 µg/mL EB) were added to the empty slide, and the coverslip was closed. Images were evaluated and recorded under a fluorescence microscope (Leica DM 1000). A minimum of 100 cells were counted at each concentration in randomly picked areas. The percentage of apoptotic cells was proportional to the total cells (27).

DNA Damage

Genotoxicity was measured by the alkaline single-cell electrophoresis method (comet assay) developed by Singh et al. (28). The comet assay method is based on different migration characteristics of DNA in the field of electricity according to different electrical charges and weights. Cells are placed in agarose and lysed. If there is no damage in DNA, the appearance of DNA is compact; it does not form any tail (comet). However, if DNA is damaged and fragmented, since these fragments have different electrical charges and molecular weights, they act differently in the electrophoretic environment. Thus, when the DNAs are stained with the fluorescent dye (i.e., ethidium bromide) they form a tailed image (28,29). To determine the genotoxic potential of ivermectin, concentrations below IC_{50} were added in 6-well plates. After 24 h incubation, cells were removed with Trypsin-EDTA and washed three times with dPBS. Cells washed with 1x PBS were centrifuged at 500x g for 5 minutes at +4 ˚C, then the supernatant was discarded. After 10 µL of cell suspension was mixed with 85 µL of 0.65% low melting point agarose, and the mixture was added to pre-coated slides with 1% normal melting point agarose (NMA), the samples were incubated for 4 hours in lysis solution at +4 °C. After incubation, the samples were washed with cold 1xdPBS and incubated for 40 minutes to open DNA bonds in the electrophoresis buffer at +4 °C. The samples were then run under electrophoresis at +4 °C for 25 minutes at 300 mA. Slides were washed three times in neutralization buffer and fixed with ethanol. The dried samples were dropped with EB (2 µg/mL), and images were taken under a fluorescence microscope (Leica DM 1000, Solms, Germany). DNA tail percentages in the images were analyzed with the Comet Assay IV analysis program (30).

Statistics Analysis

Results were given as mean ± standard deviation. Data from all experiments were analyzed for statistical significance using analysis of variance (One-Way ANOVA). IC_{50} values of ivermectin on cell lines were calculated by nonlinear regression analysis. Relationships between all parameters were analyzed with the Pearson correlation coefficient. A p-value of <0.05 was considered statistically significant. All statistical analyzes were performed using the SPSS package program (Version 25 for Windows, Chicago, USA).

Results

Cytotoxicity of Ivermectin on Breast Cancer and Healthy Breast Epithelial Cells

The effect of ivermectin after 24 h treatment on cell viability was evaluated with the luminometric ATP viability assay on BC cells (MCF7 and MDA MB231) and healthy breast epithelial cells (184A1). Before the experiments, the viability of the cells were over 95%. Treatment of ivermectin reduced cell viability in a statistically significant manner ($p<0.001$). Results in increasing doses were calculated relative to the control group (0.1% DMSO). Cytotoxicity increased dose-dependently (Figure 1). IC_{50} levels of ivermectin in cancer and healthy cells were calculated from the dose-response curve (MCF= 24.04 µM, MDA MB231= 34.12 µM, 184A1=68.51 µM).

Ivermectin's Intracellular ROS Generation Effect

In BC cells and healthy cells, a fluorescence H_2DCF-DA probe was used to examine intracellular ROS levels. Twenty four h of ivermectin treatment significantly increased intracellular ROS levels in cancer and healthy cells in a dose-dependent manner ($p<0.001$). A relatively increased amount of intracellular ROS in cancer cells was observed to be higher compared to the healthy cells (Figure 2).

Intracellular Glutathione (GSH) Level

Ivermectin lowered GSH levels in human BC cells and healthy breast epithelial cells (Figure 3). After 24 h of ivermectin treatment, intracellular GSH levels were found to decrease significantly ($p<0.001$).

Changes in Mitochondrial Membrane Potential

The mitochondrial apoptotic pathway has been explored to show the mechanisms underlying apoptotic induction in both cancer and healthy cells. Decreased MMP leads to apoptosis. After 24 h incubation of ivermectin, a statistically significant decrease ($p<0.05$) was observed using the DiOC6(3) fluorescence probe (Figure 4).

Ivermectin's Effect on Apoptosis

Apoptotic defects/disorders are critical for tumor formation and treatment resistance. Different concentrations of ivermectin under IC_{50} concentrations were imaged under fluorescence microscopy using AO/EB double dye to clarify whether cancer and healthy cells caused apoptosis after 24 h of incubation. It was found that apoptosis increased in a dose-dependent manner, and the rate of apoptosis in cancer cells was observed to be higher compared to the healthy cells (Figure 5). As the concentration increased, the increase in percentage of apoptosis was found to be statistically significant ($p<0.001$). At least 100 cells were counted at each dose, and the number of semi-quantitative apoptotic cells was calculated (Figure 6).

DNA Damage

The comet assay method was studied after 24 h treatment to evaluate the different concentrations of ivermectin below IC_{50} levels for genotoxic damage in cancer and healthy cells. Damaged DNAs were bright and comet-like, and undamaged DNAs were round and large. At least 100 cells were displayed and recorded at each concentration. The degree of damage was given as tail density %. Increasing ivermectin concentrations significantly increased DNA damage (Figure 7) ($p<0.001$). Micrographs of DNA comet images formed with increased damage are presented in Figure 8.

Discussion

The concept that ivermectin being repurposed as an anticancer agent mostly relies on the preclinical studies of the drug (6,9).

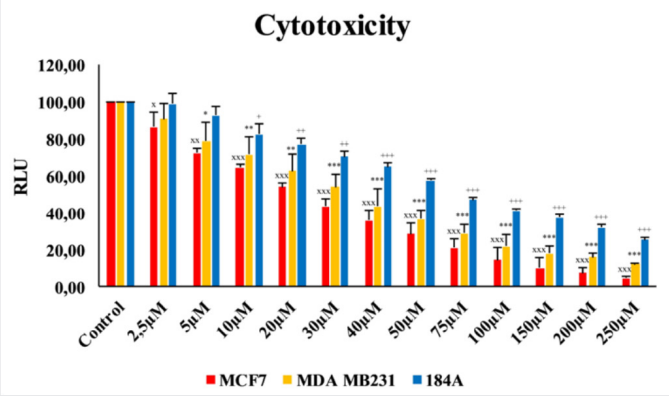

Figure 1. The effect of ivermectin on cytotoxicity. Different concentrations (2.5-250 µM) of ivermectin in MCF7, MDA MB231 and 184A1 cells were incubated for 24 hours. All results were calculated relative to the control (0.1% DMSO). Data represent four independent studies and are expressed as mean ± standard deviation. Differences in MCF7 cells, xp<0.05; xxp<0.01, xxxp<0.001; differences in MDA MB231 cells, *p<0.05; **p<0.01, ***p<0.001; differences in 184A cells, +p<0.05; ++p<0.01, +++p<0.001 values were considered statistically significant

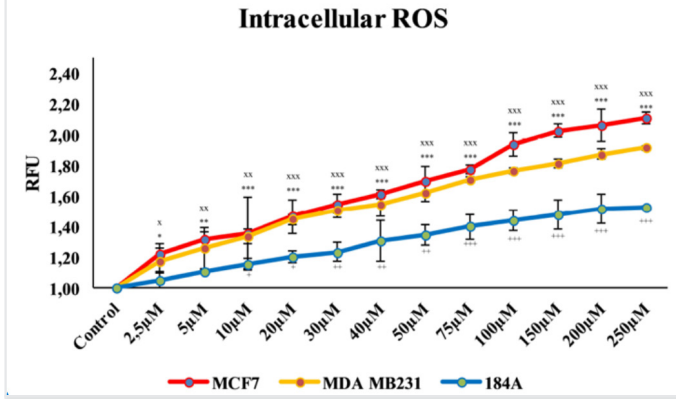

Figure 2. The effect of ivermectin on intracellular ROS level on MCF7, MDA MB231 and 184A1 cells. Ivermectin increased intracellular ROS levels in both healthy and cancer cells. Doses were calculated relative to the control and normalized with the viability level. Data represent four independent studies and are expressed as mean ± standard deviation. Differences in MCF7 cells, xp<0.05; xxp<0.01, xxxp<0.001; differences in MDA MB231 cells, *p<0.05; **p<0.01, ***p<0.001; differences in 184A1 cells, +p<0.05; ++p<0.01, +++p<0.001 values were considered statistically significant

Although it has been reported that ivermectin shows antitumoral activity through different mechanisms in various cancer cells, studies are limited, and the exact anti-tumorigenic mechanism is not yet clarified in BC. In the present study, we found that oxidative stress and DNA damage could be the underlying mechanism of ivermectin's anti-tumorigenic effects.

In this study, the IC_{50} value of ivermectin was found much higher in the healthy breast epithelium cells (184A1) compared to the BC cell lines MCF7 and MDA MB231, indicating the potential of ivermectin to be used as an anticancer agent. MCF7 is a hormone receptor-positive cell line, while MDA MB231 is a triple-negative cell line of BC (31). We found that MCF7 was more sensitive to ivermectin, and this could be due to the primary ATP synthesis route, which was oxidative phosphorylation in MCF7 while it was glycolysis in MDA MB231(32).

Juarez et al. (8,9) stated that 5 µM of ivermectin showed antitumor effects and that this concentration was clinically relevant; hence, a significant inhibition of intracellular ATP level was recorded in our study in the BC cell lines while there was no significant difference in the healthy cells. Another study with MDA MB231 revealed ivermectin's preferential inhibition of cancer cell viability (18). Dou et al. (16) tested the drug's cytotoxicity with the MTT assay using BC cell lines and found similar results, furthermore, they also found that ivermectin inhibited 60% of tumor growth

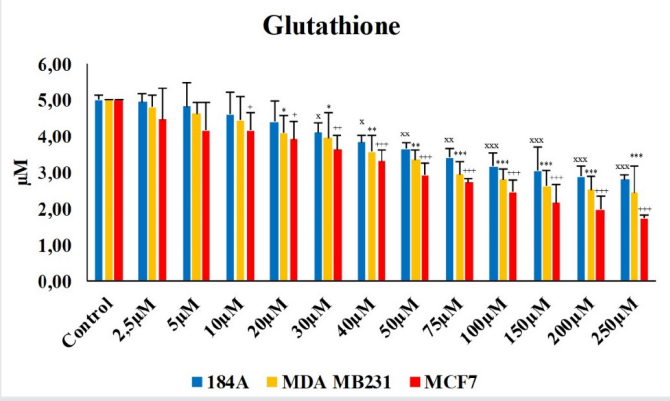

Figure 3. The effect of ivermectin on glutathione levels on MCF7, MDA MB231 and 184A1 cells. Ivermectin reduced glutathione levels in both healthy and cancer cells. Data represented four independent studies and were expressed as mean ± standard deviation. Differences in MCF7 cells, xp<0.05; xxp<0.01, xxxp<0.001; differences in MDA MB231 cells, *p<0.05; **p<0.01, ***p<0.001; differences in 184A1 cells, +p<0.05; ++p<0.01, +++p<0.001 values were considered statistically significant

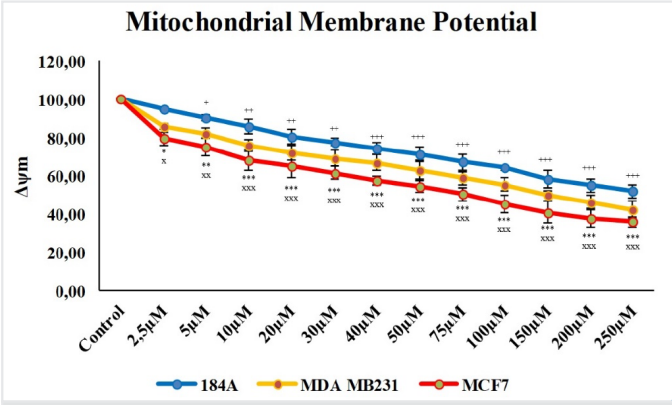

Figure 4. The effect of ivermectin on mitochondrial membrane potential on MCF7, MDA MB231 and 184A1 cells. Ivermectin reduced mitochondrial membrane potentials in both healthy and cancer cells. All doses were calculated relative to the control and normalized with the viability level. Differences in MCF7 cells, xp<0.05; xxp<0.01, xxxp<0.001; differences in MDA MB231 cells, *p<0.05; **p<0.01, ***p<0.001; ivermectin in 184A1 cells, +p<0.05; ++p<0.01, +++p<0.001 values were considered statistically significant

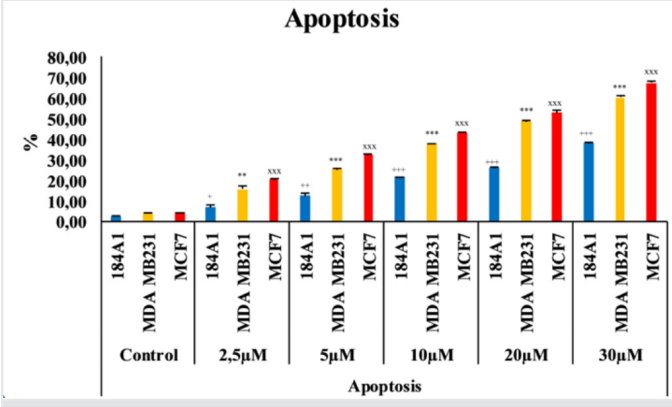

Figure 5. The effect of ivermectin on apoptosis on MCF7, MDA MB231 and 184A1 cells. Ivermectin induced apoptosis in both healthy and cancer cells. Cells counted semi-quantitative were expressed as mean ± standard deviation. Differences in MCF7 cells, xp<0.05; xx p<0.01, xxxp<0.001; differences in MDA MB231 cells, *p<0.05; **p<0.01, ***p<0.001; differences in 184A1 cells, +p<0.05; ++p<0.01, +++p<0.001 values were considered statistically significant

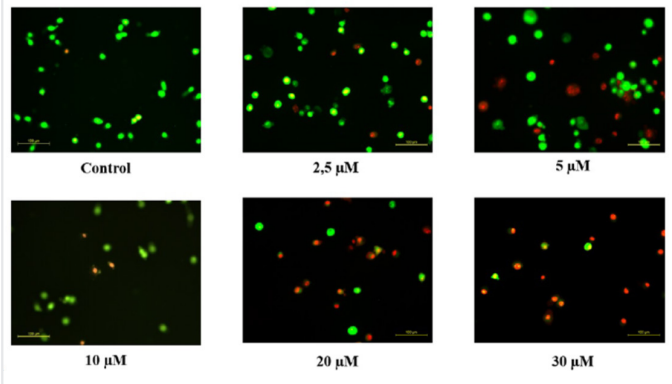

Figure 6. Effect of different concentrations of ivermectin on MCF7 cell on apoptosis. Healthy living cells in cells stained with AO/EB double dye after 24 hours were adequately structured and appeared in green; apoptotic cells appeared in yellow-orange with condensed chromatin and fragmented nucleus; necrotic cells appeared in red

AO/EB: Acridine orange/ethidium bromide

in mice. Dou et al. (16) found that 24 h ivermectin treatment to the cells did not induce apoptosis; instead, autophagy was induced. Conversely, we found that apoptosis increased in a dose-dependent manner, and the rate of apoptosis in cancer cells was observed to be higher compared to the healthy cells. In human and mouse BC cell lines, Draganov et al. (33) found that ivermectin induced apoptosis and necrosis.

Along with ATP inhibition and increased apoptosis, we found decreased MMP in a dose-dependent manner. Since oxidative phosphorylation in mitochondria is the primary source of ATP, and the MMP is a prerequisite of proper ATP synthesis, decreased MMP presumably leads to apoptosis (34). In this regard, it seemed logical that we found the MCF7 cells more sensitive to ivermectin-induced mitochondrial and oxidative stress since the cells relied on oxidative phosphorylation as the route for ATP synthesis. A study using renal cell carcinoma cell lines shows that ivermectin decreases MMP and ATP production explaining it as a consequence of mitochondrial dysfunction leading to oxidative stress (35). Liu et al. (14) also detected decreased mitochondrial membrane potential, ATP levels, and increased mitochondrial superoxide in ivermectin-treated glioblastoma cells. These inhibitory effects of ivermectin were significantly reversed in these studies when the cells were treated with antioxidants, which supported the presence of ivermectin-induced oxidative stress.

The ROS produced in large quantities can activate cell death signaling pathways; furthermore, ROS accumulation and disruption of MMP in the presence of cellular stress can cause the inner membrane to break down leading to apoptosis (36). Besides increased ROS levels in our study, decreased levels of glutathione might pave the way to oxidative stress formation, which as a result, might cause mitochondrial damage and subsequently cell death. Zhu et al. (35) detected that ivermectin caused oxidative stress and DNA damage in ivermectin-treated renal carcinoma cells. It is known that DNA damage is an efficient factor that can induce cell death. Zhang et al. (13) suggested that ivermectin induced apoptosis via the mitochondrial pathway by recording ROS formation and MMP disruption along with DNA damage in ivermectin-treated HeLa cells. In our study, after ivermectin treatment DNA damage was more in the cancer cells compared to the healthy cells, and especially the cells with increased oxidative stress were seen to have more DNA damage.

Additionally, besides the potential anticancer effects, ivermectin can be considered to be used in combination with approved anticancer drugs of which resistance is a big problem to solve. Jiang et al. (37) and Kwon et al. (38) found that ivermectin could reverse drug resistance in cancer cells .

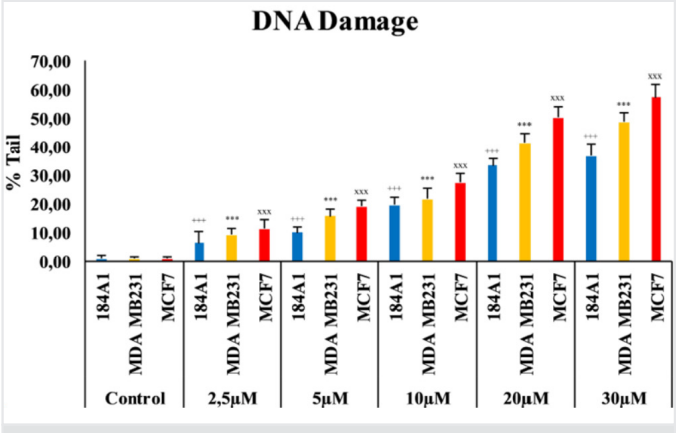

Figure 7. The effect of ivermectin on DNA damage on MCF7, MDA MB231, and 184A1 cells. Ivermectin increased DNA damage, in other words, genotoxicity, in both healthy and cancer cells. Results were given as % tail density and expressed as mean ± standard deviation

Conclusion

In conclusion, ivermectin induces apoptosis via oxidative stress and DNA damage in BC cells. The *in vitro* mechanistic studies of promising anticancer agents for repurposing are essential guides for drug developers.

Acknowledgments

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Ethics

Ethics Committee Approval: *In vitro* study.

Informed Consent: *In vitro* study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: E.M.G., Concept: E.M.G., Design: E.M.G., Data Collection or Processing: E.M.G., A.G.A., Analysis or Interpretation: E.M.G., A.G.A., Literature Search: E.M.G., A.G.A., Writing: E.M.G., A.G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

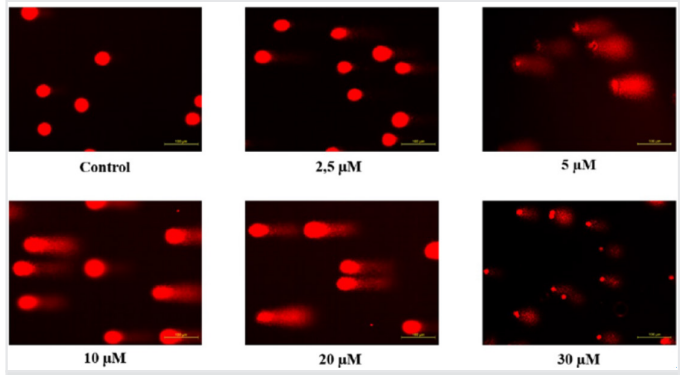

Figure 8. Effect of different concentrations of ivermectin on MCF7 cell on DNA damage. The comet image in the DNA formed after the damage increased in a dose-dependent manner

References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Cancer Today (powered by GLOBOCAN 2018). IARC CancerBase 2018;15.
2. Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA 2019;321:288-300.
3. Anastasiadi Z, Lianos GD, Ignatiadou E, Harissis HV, Mitsis M. Breast cancer in young women: an overview. Updates Surg 2017;69:313-7.
4. Harbeck N, Gnant M. Breast cancer. Lancet 2017;389:1134-50.
5. Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature 2012;486:346-52.
6. Antoszczak M, Markowska A, Markowska J, Huczyński A. Old wine in new bottles: Drug repurposing in oncology. Eur J Pharmacol 2020;866:172784.
7. Lindley D. Merck's new drug free to WHO for river blindness programme. Nature 1987;329:752.
8. Juarez M, Schcolnik-Cabrera A, Dominguez-Gomez G, Chavez-Blanco A, Diaz-Chavez J, Duenas-Gonzalez A. Antitumor effects of ivermectin at clinically feasible concentrations support its clinical development as a repositioned cancer drug. Cancer Chemother Pharmacol 2020;85:1153-63.
9. Juarez M, Schcolnik-Cabrera A, Dueñas-Gonzalez A. The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug. Am J Cancer Res 2018;8:317-31.
10. Hashimoto H, Messerli SM, Sudo T, Maruta H. Ivermectin inactivates the kinase PAK1 and blocks the PAK1-dependent growth of human ovarian cancer and NF2 tumor cell lines. Drug Discov Ther 2009;3:243-6.
11. Sharmeen S, Skrtic M, Sukhai MA, Hurren R, Gronda M, Wang X, et al. The antiparasitic agent ivermectin induces chloride-dependent membrane hyperpolarization and cell death in leukemia cells. Blood 2010;116:3593-603.
12. Nambara S, Masuda T, Nishio M, Kuramitsu S, Tobo T, Ogawa Y, et al. Antitumor effects of the antiparasitic agent ivermectin via inhibition of Yes-associated protein 1 expression in gastric cancer. Oncotarget 2017;8:107666-77.
13. Zhang P, Zhang Y, Liu K, Liu B, Xu W, Gao J, et al. Ivermectin induces cell cycle arrest and apoptosis of HeLa cells via mitochondrial pathway. Cell Prolif 2018;52:e12543.
14. Liu Y, Fang S, Sun Q, Liu B. Anthelmintic drug ivermectin inhibits angiogenesis, growth and survival of glioblastoma through inducing mitochondrial dysfunction and oxidative stress. Biochem Biophys Res Commun 2016;480:415-21.
15. Melotti A, Mas C, Kuciak M, Lorente-Trigos A, Borges I, Ruiz i Altaba A. The river blindness drug Ivermectin and related macrocyclic lactones inhibit WNT - TCF pathway responses in human cancer. EMBO Mol Med 2014;6:1263-78.
16. Dou Q, Chen HN, Wang K, Yuan K, Lei Y, Li K, et al. Ivermectin induces cytostatic autophagy by blocking the PAK1/Akt Axis in breast cancer. Cancer Res 2016;76:4457-69.
17. Wang K, Gao W, Dou Q, Chen H, Li Q, Nice EC, et al. Ivermectin induces PAK1-mediated cytostatic autophagy in breast cancer. Autophagy 2016;12:2498-9.
18. Dominguez-Gomez G, Chavez-Blanco A, Medina-Franco JL, Saldivar-Gonzalez F, Flores-Torrontegui Y, Juarez M, et al. Ivermectin as an inhibitor of cancer stem-like cells. Mol Med Rep 2018;17:3397-403.
19. Kwon YJ, Petrie K, Leibovitch BA, Zeng L, Mezei M, Howell L, et al. Selective inhibition of SIN3 corepressor with avermectins as a novel therapeutic strategy in triple-negative breast cancer. Mol Cancer Ther 2015;14:1824-36.
20. Crouch SPM, Kozlowski R, Slater KJ, Fletcher J. The use of ATP bioluminescence as a measure of cell proliferation and cytotoxicity. J Immunol Methods 1993;160:81-8.
21. Kocyigit A, Guler EM, Karatas E, Caglar H, Bulut H. Dose-dependent proliferative and cytotoxic effects of melatonin on human epidermoid carcinoma and normal skin fibroblast cells. Mutat Res - Genet Toxicol Environ Mutagen 2018;829:50-60.
22. Wu T, Qiang L, Chen FH, Zhao Q, Yang Z, Zou MJ, et al. LFG-500, a newly synthesized flavonoid, induced a reactive oxygen species-mitochondria-mediated apoptosis in hepatocarcinoma cells. Biomed Prev Nutr 2011;1:132-8.
23. Günes-Bayir A, Kiziltan HS, Kocyigit A, Güler EM, Karataş E, Toprak A. Effects of natural phenolic compound carvacrol on the human gastric adenocarcinoma (AGS) cells in vitro. Anticancer Drugs 2017;28:522-30.
24. Rottenberg H, Shaolong W. Quantitative assay by flow cytometry of the mitochondrial membrane potential in intact cells. Biochim Biophys Acta - Mol Cell Res 1998;1404:393-404.
25. McGahon AJ, Martin SJ, Bissonnette RP, Mahboubi A, Shi Y, Mogil RJ, et al. The end of the (cell) line: methods for the study of apoptosis in vitro. Methods Cell Biol 1995;46:153-85.
26. Kasibhatla S. Acridine Orange/Ethidium Bromide (AO/EB) Staining to Detect Apoptosis. Cold Spring Harb Protoc 2006:pdb.prot4493-pdb.prot4493.
27. Kocyigit A, Guler EM. Curcumin induce DNA damage and apoptosis through generation of reactive oxygen species and reducing mitochondrial membrane potential in melanoma cancer cells. Cell Mol Biol (Noisy-le-grand) 2017;63:97-105.
28. Singh NP, Danner DB, Tice RR, Brant L, Schneider EL. DNA damage and repair with age in individual human lymphocytes. Mutat Res DNAging 1990;237:123-30.
29. Demirbag R, Yilmaz R, Gur M, Kocyigit A, Celik H, Guzel S, et al. Lymphocyte DNA damage in patients with acute coronary syndrome and its relationship with severity of acute coronary syndrome. Mutat Res - Fundam Mol Mech Mutagen 2005;578:298-307.
30. Hartmann A, Agurell E, Beevers C, Brendler-Schwaab S, Burlinson B, Clay P, et al. Recommendations for conducting the in vivo alkaline Comet assay. Mutagenesis 2003;18:45-51.
31. Holliday DL, Speirs V. Choosing the right cell line for breast cancer research. Breast Cancer Res 2011;13:1-7.
32. Theodossiou TA, Ali M, Grigalavicius M, Grallert B, Dillard P, Schink KO, et al. Simultaneous defeat of MCF7 and MDA-MB-231

resistances by a hypericin PDT–tamoxifen hybrid therapy. npj Breast Cancer 2019;5:1-10.

33. Draganov D, Gopalakrishna-Pillai S, Chen YR, Zuckerman N, Moeller S, Wang C, et al Modulation of P2X4/P2X7/ Pannexin-1 sensitivity to extracellular ATP via Ivermectin induces a non-apoptotic and inflammatory form of cancer cell death. Sci Rep 2015;5:16222.
34. Zorova LD, Popkov VA, Plotnikov EY, Silachev DN, Pevzner IB, Jankauskas SS, et al. Mitochondrial membrane potential. Anal Biochem 2018;552:50-9.
35. Zhu M, Li Y, Zhou Z. Antibiotic ivermectin preferentially targets renal cancer through inducing mitochondrial dysfunction and oxidative damage. Biochem Biophys Res Commun 2017;492:373-8.
36. Hargreaves IP, Al Shahrani M, Wainwright L, Heales SJR.Drug-Induced Mitochondrial Toxicity. Drug Saf 2016;39:661-74.
37. Jiang L, Wang P, Sun Y-J, Wu Y-J. Ivermectin reverses the drug resistance in cancer cells through EGFR/ERK/Akt/NF-κB pathway. J Exp Clin cancer Res 2019;38:265.
38. Kwon YJ, Petrie K, Leibovitch BA, Zeng L, Mezei M, Howell L, et al (2015) Selective inhibition of SIN3 corepressor with avermectins as a novel therapeutic strategy in triple negative breast cancer HHS Public Access. Mol Cancer Ther 2015;14:1824-36.

Original Article

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The Medicinal Effects of Different Solvent Extracts of *Pyracantha Coccinea* Roem. Fruits: Heavy Metal Content, Antioxidant, and Antimicrobial Properties

Pyracantha Coccinea Roem. Meyvelerinin Farklı Çözücü Ekstraktlarının Tıbbi Etkileri: Ağır Metal İçeriği, Antioksidan ve Antimikrobiyal Özellikler

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ABSTRACT

Objective: The current investigation has been conducted to assess the total flavonoid content, total phenolic content, heavy metal composition, and antioxidant and antimicrobial activities of *Pyracantha coccinea* Roem. fruit extracts prepared with different solvents.

Methods: Ethanol, diethyl ether, and hot water extraction were used as solvents to prepare the extract of *Pyracantha coccinea* Roem. fruit. Total phenolic ingredient was assessed by Folin-Ciocalteu assay, and the total ingredient of flavonoids was measured spectrophotometrically via $AlCl_3$ assay. The antioxidant activities of the extracts were investigated via free radical scavenging assays, DPPH, and ABTS. The fruits were analyzed by Inductively Coupled Plasma/Mass Spectrometer to determine heavy metal content. The antimicrobial activities of the extracts were investigated using agar well diffusion method against *Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus cereus,* and *Candida albicans*.

Results: It was determined that the total flavonoid ingredient, total phenolic ingredient, ABTS and DPPH activities of the hot water extract were significantly higher than the other fractions. These parameters were found to be significantly higher in ethanol extract compared to ether extract. All extracts exhibited antimicrobial activity against *Bacillus cereus* and *Pseudomonas aeruginosa* while the hot water fraction exhibited the highest antibacterial effect against *Pseudomonas aeruginosa*. It was determined that Cr, Co, Ni, and Cu contents exceeded the toxicity thresholds that might be found in plants.

ÖZ

Amaç: Mevcut araştırma, farklı çözücülerle hazırlanan *Pyracantha coccinea* Roem. meyve ekstraktlarının toplam flavonoid içeriği, toplam fenolik içeriği, ağır metal bileşimi ve antioksidan ve antimikrobiyal aktivitelerini değerlendirmek için yapılmıştır.

Yöntemler: *Pyracantha coccine*a Roem. meyvesinin ekstraktını hazırlamak için çözücü olarak etanol, dietil eter ve sıcak su ekstraksiyonu kullanıldı. Toplam fenolik bileşen Folin-Ciocalteu yöntemi ile toplam flavonoidlerin içerik $AlCl_3$ yöntemi ile spektrofotometrik olarak ölçüldü. Ekstraktların antioksidan aktiviteleri, serbest radikal süpürme deneyleri, DPPH ve ABTS ile araştırıldı. Meyveler, ağır metal içeriğini belirlemek için İndüktif Eşleşmiş Plazma-Kütle Spektrometresi ile analiz edildi. Ekstraktların antimikrobiyal aktiviteleri, *Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus cereus* ve *Candida albicans*'a karşı agar kuyusu difüzyon yöntemi kullanılarak araştırıldı.

Bulgular: Sıcak su ekstraktının toplam flavonoid bileşeninin, toplam fenolik bileşeninin, ABTS ve DPPH aktivitelerinin diğer fraksiyonlara göre anlamlı derecede yüksek olduğu belirlendi. Bu parametrelerin etanol ekstraktında eter ekstraktından önemli ölçüde daha yüksek olduğu bulundu. Tüm ekstreler *Bacillus cereus* ve *Pseudomonas aeruginosa*'ya karşı antimikrobiyal aktivite sergilerken, sıcak su fraksiyonu *Pseudomonas aeruginosa*'ya karşı en yüksek antibakteriyel etkiyi sergiledi. Cr, Co, Ni ve Cu içeriklerinin bitkilerde bulunabilecek toksisite eşiklerini aştığı belirlendi.

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Conclusion: These results suggest that *Pyracantha coccinea* Roem. fruit may be considered as a natural source of antioxidants and antimicrobial agents.

Keywords: ABTS, antimicrobial activity, antioxidant activity, DPPH, *Pyracantha coccinea* Roem.

Sonuç: Bu sonuçlar, *Pyracantha coccinea* Roem. meyvesinin doğal bir antioksidan ve antimikrobiyal ajan kaynağı olarak kabul edilebileceğini göstermektedir.

Anahtar Kelimeler: ABTS, antimikrobiyal aktivite, antioksidan aktivite, DPPH, *Pyracantha coccinea* Roem.

Introduction

Reactive oxygen species (ROS) are produced in oxidative metabolism, which is required to generate the energy needed by most living organisms and to fuel other biological processes. On the other hand, overproduced ROS harm cells by affecting proteins and causing damage to DNA. Therefore, ROS have significant effects on the pathogenesis of numerous diseases such as cancer, neurodegenerative disorders, cardiovascular diseases, atherosclerosis, inflammation, and cataracts (1). Natural antioxidants have extensive variety of biological activities such as alteration of intracellular redox potential, prevention of ROS formation, and direct or indirect scavenging of free radicals. Antioxidants are essential for the survival of living organisms against injuries provoked by uncontrolled manufacturing of ROS and accompanying protein damage, lipid peroxidation, and DNA chain breakage. In addition, antioxidants contribute to the inhibition of degenerative disorders by preventing the oxidation of other molecules. However, it has been reported that the intake of natural antioxidants such as polyphenol-rich nutrients, vegetables, and fresh fruits can resist oxidative deterioration of free radicals (2).

Phytochemical antioxidants are important in therapeutic applications against animal and human pathogens including fungi, bacteria, and viruses. These secondary metabolites which are produced by plants are highly structurally diverse organic chemicals which are used in the nutraceutical industry that play various functions including bactericidal, bacteriostatic, antimicrobial, and chemotherapeutic functions (3). Plants (herbs, vegetables, and fruits) possess extensive diversity of free radical scavenger molecules such as nitrogen compounds, vitamins, phenolic compounds, terpenoids, and other endogenous metabolites which are abundant in antioxidant activities (2). Flavonoids contain tannins and phenolic acids. All these active ingredients can act as antioxidants through lipid oxidation prevention, radical scavenging, or reduction power. Flavonoids have antiproliferative, antitumor, antifungal, anti-inflammatory, antiviral, and antibacterial features (4). In this regard, screening plants for their antimicrobial properties pose significant potential to discover novel compounds for medicinal usage (5). On the other hand, it should be known that when medicinal plants are used in the treatment of certain diseases, they may be toxic besides their pharmacological effect if their heavy metal content increases. Although the efficacy of medicinal plants is mainly associated with their components such as secondary metabolites and essential oils, heavy metals such as Ni, Pb, Zn, Cd, and other impurities are thought to cause health problems if they are above threshold concentrations (6).

There are recent studies on many herbs which produce health boosting effects such as antimicrobial properties and antioxidant properties, yet the potential of many herbs as sources for novel medicine still remain uninvestigated (5). Pyracantha (firethorn) is a genus belonging to Rosaceae family (Amygdaloideae subfamily, tribe Maleae) with various species and hybrids scattered throughout Eurasia. *Pyracantha coccinea* Roem. (Red pyracantha) is a thorny shrub that grows up to 3 m in height at different altitudes in China, Himalayas (4), Italy, and Turkey. It has small bright red, fruits which may be cooked for marmalades, jams, jellies, and sauces. In addition, its fruits are used in conventional medicine for their cardiac, tonic and diuretic features (7).

Pyracantha coccinea Roem. fruit extracts have rarely been explored for their phytochemical properties and biological effects when prepared with different solvents. Therefore, the purposes of this research are: 1) to investigate the total phenol, total flavonoid, and heavy metal contents of *Pyracantha coccinea* Roem. fruits extracted with different solvents (ethanol, diethyl ether, and hot water); and 2) to assess the antimicrobial and antioxidant activities of *Pyracantha coccinea* Roem. fruits.

Methods

Plant samples: *Pyracantha coccinea* Roem. fruit samples were collected and identified from Aksaray in September 2020. The Flora of Turkey and The East Aegean Islands (8) and the Checklist of the Flora of Turkey - Vascular Plants (9) were used for identification of the plant specimens. The plant species was identified at Anadolu University Plant Medicine and Scientific Research Center. They were preserved in Aksaray University Herbarium with the code of M. Tekşen 2982 (Aksu). The fruit parts of the collected plants were separated and washed with and then rinsed in distilled water. Afterwards, the fruits were dried in shade at room temperature and powdered.

Preparation of plant extracts: Powdered fruit particles were used to obtain *Pyracantha coccinea* Roem. fruit extracts. Three solvents were preferred for the extraction: ethanol, diethyl ether, and hot water (100 °C). 300 mL of solvent was added on 50 g of fruit particles in all three extractions. The extracts were kept in an ultrasonic sonicator (Bandelin Sonorex) at 37 °C for 30 minutes. Next, they were kept in the shaker for a total extraction duration of 24 hours. Then the plant particles were removed from the solvent with the help of a paper coarse filter. After the ether and ethanol were removed from the extracts prepared with ether and ethanol, they were re-dissolved in ethanol (50 mL). The other extract was centrifuged at 8,000 g for 10 minutes. The acquired extracts were maintained at +4 °C to be used in measurements.

Total phenolic content measurement: Total phenolic matter analysis was assayed based on the Folin-Ciocalteu method with minor modifications (10) by adding 900 µL of distilled water and 5 mL of 0.2 M Folin-Ciocalteu reagent onto 100 µL of the extract. After adding 5mL (7.5%) of Na_2CO_3 and incubation for 2 hours at room temperature, the absorbance was determined at a wavelength of about 760 *nm* in a spectrophotometer (Biochrom S70 Dual). Gallic acid was used to prepare a standard curve. The data are stated as mg gallic acid equivalent per g dry plant weight (DW).

Total flavonoid content measurement: Total flavonoid substance was determined based on in the assay developed by Dewanto et al. (11) with minor modifications using $AlCl_3$ and $NaNO_2$ as reagents. 4 mL of pure water and 0.3 mL of $NaNO_2$ (5%) were added onto 0.4 mL of extract and incubated for 5 minutes. Then 0.5 mL of 10% $AlCl_3$ was added to the mixture and kept for 6 more minutes. Next, the absorbance of the mixture, into which 2 mL of 1M NaOH and 3 mL of distilled water were added, was read at 510 nm in a spectrophotometer (Biochrom S70 Dual). Catechin concentrations 0.01-0.25 mg/mL were used to generate a calibration curve, and the results were stated as mg catechin equivalent per g DW.

Assay of DPPH scavenging activity: Free radical scavenging activity of *Pyracantha coccinea* Roem. fruit extracts was measured based on DPPH assay previously carried out by Brand-Williams et al. (12) with minor modifications (12). A 25 mg/L DPPH solution was prepared with methanol. After adding 0.1 mL of extract to 3.9 mL of DPPH solution, it was kept in a shaker in a dark environment at room temperature for 30 minutes. Absorbance measurements were conducted at 517 nm wavelength in a spectrophotometer (Biochrom S70 Dual). The calculations were performed using the formula below.

DPPH radical scavenging %=$[(A_C-A_E)/A_C x100]$

The A_C is the absorbance of DPPH solution, and A_E is the absorbance of the sample.

Assay of ABTS scavenging activity: The antioxidant capacities of the samples were determined based on the spectrophotometric measurement method developed by Re et al. (13) with slight changes. Briefly, a 2,2′-Azinobis-(3-Ethylbenzthiazolin-6-Sulfonic Acid) ($ABTS^+$) cation radical solution was produced by reacting ABTS (2 mM) in H_2O and $K_2S_2O_8$ solution (final concentration: 2.45 mM) for 12 hours in dark at room temperature. Before $ABTS^+$ radical solution was used, the absorbance of the control solution at 734 nm was adjusted to a value between 0.750 nm-0.800 nm with phosphate buffer with 0.1 M and pH 7.4. 1 mL of ABTS solution was added on 80 µL of extract samples in different concentrations, and the total volume was completed to 4 mL with phosphate buffer. These samples were incubated for 30 minutes by vortexing, and their absorbance was evaluated at 734 nm via a spectrophotometer (Biochrom S70 Dual). ABTS radical scavenging activity inhibition percentages were calculated with the formula given below:

% ABTS Inhibition=$[(A_C-A_E)/A_C x100]$

The A_C is the absorbance of ABTS solution, and A_E is the absorbance of the sample.

Profiling of mineral elements in *Pyracantha coccinea* Roem. Fruit: The analysis of heavy metals (Cr, Cd, Mn, Pb, Fe, Ni, Co, Zn, As, and Cu) in *Pyracantha coccinea* Roem. fruits were performed by an Inductively Coupled Plasma/Mass Spectrometer (ICP-MS) based on the method by Hajar et al. (14) with minor changes. Approximately 0.2 g of plant sample was put into the microwave tube, and 10 mL of nitric acid was added on it. The solution mixture was mixed and kept for 10 minutes for preburning. Later, the tubes were covered and exposed to heat in a microwave system. Initially, the microwave was heated up to 190 °C for 20 minutes. Then it was kept at 190 °C for 15 minutes. The pressure was set at 800 psi and the power at 900-1800 watts. Next, it was cooled from 190 °C down to room temperature in 15 minutes. The samples that were taken from the tubes after burning were completed up to 50 mL with ultrapure water. A CEM MARS6 model microwave oven was used for microwave-assisted digestion of the plant material. The heavy metal contents in the examined plant material were analyzed using Bruker Aurora M90 ICP-MS. Firstly, a standard and a blank were read for each heavy metal content using ICP-MS instrument. The calibration solutions were prepared by the suitable dilution of the single element certified reference materials. Then the calibration charts were plotted. Later, the samples and blind of the samples were analyzed by reading. The operating conditions of ICP-MS instrument are given in Table 1.

Bacterial and fungal strains and culture conditions: The pathogenic microorganisms which were studied in the investigation were produced from the microbial culture collection at Aksaray University Scientific and Technological Application and Research Center Microbiology Laboratory. *Pseudomonas aeruginosa* (ATCC 27853), *Bacillus cereus* (ATCC 10231), and *Staphylococcus aureus* (ATCC 25923) were grown using Brain Heart Infusion Broth (BHI) (Merck) medium. *Candida albicans* (ATCC 10231) strain was investigated for antifungal activity. The microorganisms which were to be tested were grown in Mueller Hinton broth overnight in a rotary shaker at 37 °C. Every strain in the present study was used after adjusting it at

Table 1. Operating conditions of ICP-MS instrument

Parameters	
RF power (kW)	1.40
Plasma Gas Flow Rate (L min^{-1})	15
Auxiliary Gas Flow Rate (L min^{-1})	1.5
Sheath Gas Flow Rate (L min^{-1})	0.11
Nebulizer Gas Flow Rate (L min^{-1})	0.95
Read delay (sn)	40
Gas	Argon
Purge gas	Hydrogen
Repeat/sample reading	5
Scan replicate	5
Scan mode	Peak hopping
Hydrogen Gas Flow Rate (mL min^{-1})	80

ICP-MS: Inductively Coupled Plasma/Mass Spectrometer

a concentration of 10^8 cells/mL with a 0.5 McFarland standard (15). *Candida albicans* was prepared from a 48-hours culture of fungal isolates in potato dextrose broth (16). The fungal spore density at a final concentration of 10^6 spores/mL was acquired using a spectrophotometer (595 nm). Each microorganism was kept by subculturing regularly on BHI medium and storing at +4 °C before being used in the tests.

Analysis of Antimicrobial Activities of *Pyracantha Coccinea* Roem. Fruits: The antimicrobial effects of *Pyracantha coccinea* Roem. fruit extracts on various pathogenic bacteria and fungi were investigated by agar well diffusion method. The agar well diffusion assay was used to monitor the antifungal and antibacterial activities of various solvent extracts (17). A 100 µL of fresh bacterial or fungal culture was inoculated in the middle of a sterile petri dish with a Mutueller hinton agar medium, and smear was performed. Wells were made into microorganism seeded media using a sterile cork borer (5 mm diameter). Next, 20 µL of each extract (20% w/v concentration if any residual) was added to the respective wells. The prepared plates were kept in the refrigerator for 30 minutes to ensure that the extracts penetrated the agar thoroughly. Then the petri dishes were incubated at 37 °C for 24 hours. The antimicrobial activity was determined by assessing the zone of inhibition (containing well diameter) that appeared after the incubation period. Gentamicin (10 UI) was used as a positive control, while Dimethyl sulfoxide (DMSO at 10% concentration) was used as a negative control. All tests were done three times.

Statistical Analysis

Data analyses were performed with Statistical Package for Social Sciences (SPSS) version 18.0 statistical software package (SPSS Inc, Chicago, Illinois). Statistical significance was verified by One-Way analysis of variance (ANOVA) with Tukey's post-hoc test. The outcomes were presented as means ± standard deviation (n=3 per each test sample). The differences between the applied doses with $p<0.05$ was recognized as statistically significant.

Results

Figure 1 exhibits the total phenolic ingredient and total flavonoid ingredient of *Pyracantha coccinea* Roem. fruit extracted with various solvents. Among *Pyracantha coccinea* Roem. fruit extracts prepared with the solvents, the highest content of phenolic compounds was found in hot water extracts in comparison to the ethanol and diethyl ether extracts ($p<0.001$, $p<0.001$). However, the total phenolic content in the ethanol extract was found to be higher than the diethyl ether extract ($p<0.001$). The extraction with hot water showed the highest total flavonoid content compared to the ethanol and diethyl ether extracts ($p<0.001$, $p<0.001$, respectively). However, the total flavonoid content was found to be higher in the ethanol extract compared to the diethyl ether extract ($p<0.001$).

The outcomes for ABTS free radical scavenging activity of *Pyracantha coccinea* Roem. fruit extracts are provided in Figure 2A. The hot water extracts exhibited higher ABTS values with higher radical scavenging activity compared to the ethanol and diethyl ether extracts ($p<0.001$, $p<0.001$). ABTS values were found to be lower in the diethyl ether extract compared to the ethanol extract ($p<0.001$). As shown in Figure 2B, the highest DPPH scavenging ability among *Pyracantha coccinea* Roem. fruit extracts were obtained in hot water compared to the ethanol and diethyl ether extract ($p<0.001$ and $p<0.001$, respectively). DPPH scavenging level was found to be lower in the diethyl ether extract compared to the ethanol extract ($p<0.001$).

The outcomes of antimicrobial activity against the tested microorganisms are summarized in Table 2. The extracts of *Pyracantha coccinea* Roem. fruit in different solvents exhibited antimicrobial activities against *Bacillus cereus* and *Pseudomonas aeruginosa*. In *Bacillus cereus*, there were no significant differences in the levels of antimicrobial activity in different solvent extract applications with *Pyracantha coccinea* Roem. fruit ($p>0.05$). On the other hand, *Pyracantha coccinea* Roem. fruit hot water extract displayed *antimicrobial activity higher* than ethanol and diethyl ether extracts ($p<0.01$, $p<0.01$).

The present study also determined the contents of heavy metal elements Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Mo, Cd, and Pb in *Pyracantha coccinea* Roem. fruit (Table 3). The presences of Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Mo, and Pb were confirmed, and

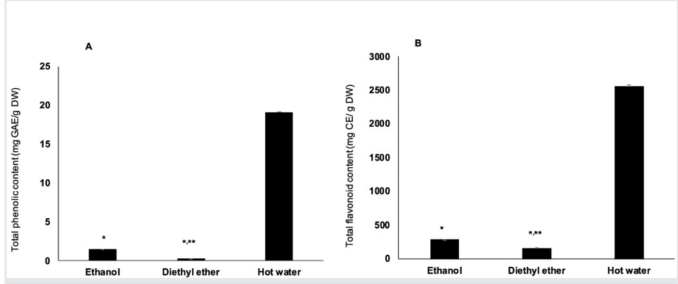

Figure 1. Total phenol (A) and total flavonoid (B) contents of *Pyracantha coccinea* Roem. fruit extracts prepared with various solvents. The results are expressed as means ± standard deviation from three independent experiments. *Indicates $p<0.001$ versus hot water extract, and **Indicates $p<0.001$ versus ethanol extract

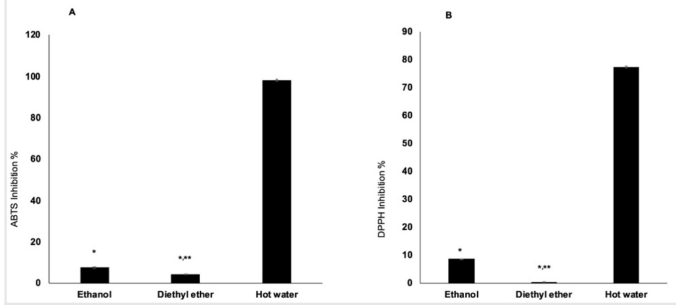

Figure 2. Antioxidant properties of *Pyracantha coccinea* Roem. fruit extracts prepared with various solvents: ABTS radical scavenging activity (A) and DPPH radical scavenging activity (B). The results are expressed as means ± standard deviation from three independent experiments. *Indicates $p<0.001$ versus hot water extract, and **Indicates $p<0.001$ versus ethanol extract

their concentrations were defined. However, Cd was not detected. The heavy metal contents of *Pyracantha coccinea* Roem. fruits were evaluated with reference to the normal and toxic heavy metal concentrations found in previously studied medicinal plants (6). Consequently, it was determined that Mn, Fe, Zn, As, Mo, Cd, and Pb concentrations in *Pyracantha coccinea* Roem. fruit were within the safety limits while Cr, Co, Ni and Cu concentrations were above the safety limits.

Discussion

There is a lot of existing evidence on the effects of free radicals on the formation of a number of disorders such as neurodegeneration, some inflammatory diseases, and cancer (18). Although there is an antioxidant defense system in human body, it is often insufficient to neutralize multiple attacks that increasingly affect the body. In order to maintain a balance among antioxidants and oxidants in the body, substances that are effective against ROS are used as nutritional support. On the other hand, the consumption of some artificial antioxidants has been recently suggested to be limited due to their carcinogenic and toxic effects (19). Because of toxicological apprehensions related with synthetic preservatives and antioxidants, the antioxidant and antimicrobial effects of numerous curative herbs are being studied worldwide (18). Plants include some phytochemicals such as alkaloids, flavonoids, terpenoids, and vitamins, which have antioxidant and antimicrobial properties (7). Antioxidant substances and phytochemicals in plant samples are often influenced by diverse conditions such as time, temperature, solvent concentration, and solvent polarity during extraction and purification. Therefore, the diverse phytochemicals are extracted in solvents of varied polarity because one single solvent may not be sufficient to extract all phytochemicals (20). Accordingly, the present study aims to define the heavy metal composition, total flavonoid and total phenolic ingredients and to investigate the antimicrobial and antioxidant activities of *Pyracantha coccinea* Roem. fruits obtained with different solvents.

Antioxidants are very crucial because of their capability of neutralizing free radicals (18). Polyphenols with antioxidant functions can preserve cells from oxidative injury and hence decrease the risk of numerous degenerative illnesses related with oxidative stress caused by free radicals (19). Phenolic compounds have hydroxyl groups in their structures and are important plant components due to their free radical neutralizing capacity through these groups. Therefore, the total phenolic content can be utilized as a basis for rapid determination of antioxidant capacity (18). The phenolic compounds of plants are divided into several categories, and the leading compounds are flavonoids with strong antioxidant activities. It is known that the flavonoids which are found naturally in plants have significant positive effects on human health. Investigations on flavonoid derivatives have revealed an extensive variety of antiviral, antibacterial, anticancer, anti-inflammatory, and anti-allergic activities. Flavonoids have been shown to be very effective scavengers for most oxidizing molecules and to contain various free radicals and singlet oxygen which play a beneficial role against various diseases (21). The total flavonoid and phenolic ingredients

Table 2. Antimicrobial effect of *Pyracantha coccinea* Roem. fruit extracts prepared with different solvents against *Bacillus cereus* (ATCC 10231), *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853), and *Candida albicans* (ATCC 10231) demonstrated by Agar well diffusion method

Microorganisms	Ethanol	Diethyl ether	Hot water
Bacillus cereus	7.00±0.001^{ns}	5.67±0.58^{ns}	7.3333±1.16^{ns}
Staphylococcus aureus	-	-	-
Pseudomonas aeruginosa	5.33±0.58*	5.00±0.00*	7.33±0.58
Candida albicans	-	-	-

The results are expressed as means ± SD from three independent experiments. *Indicates $p<0.01$ versus hot water extract. $^{ns}p>0.05$ indicates statistically insignificant

Table 3. Total content of heavy metals (mg kg-1) of *Pyracantha coccine*a Roem. fruit and reference values for trace elements as normal and toxic concentrations in plants

Element	*Pyracantha coccinea* Roem. fruit heavy metals content (mg kg-1)	Normal concentrations in plants[10] (mg kg-1)	Toxic concentrations in plants[10] (mg kg-1)
Cr	116.38±0.03	<0.1-1	2
Mn	31.32±0.06	15-100	400
Fe	58.48±0.41	50-250	(>500)
Co	27.08±0.31	0.05-0.5	30-40
Ni	669.72±1.75	0.1-5	30
Cu	531.08±3.89	3-15	20
Zn	26.28±0.7	15-150	200
As	22.12±0.45	10-60	<2
Cd	Not detected	<0.1-1	10
Pb	1.8±0.45	1-5	20

in the extracts are also determined to predict the relationship between the free radical scavenging activity and the polyphenolic ingredient (22). Thus, the total phenolic and flavonoid contents in *Pyracantha coccinea* Roem. fruit extracts were explored in the present study. The amount of ingredients was observed to differ in the extracts prepared with the different solvents used. The data obtained from the analyzes showed that there was a statistical difference in total flavonoid and phenolic contents of the extracts prepared with various solvents. In the current study, hot water extract displayed the highest total phenolic content and had the best antioxidant capacity compared to the other two extracts. The amount of total phenolic substance was found to be higher in ethanol extract than diethyl ether extract. In the study conducted by Keser (23), the highest total phenolic content among the firefly extracts prepared with various solvents was detected in the extract prepared with ethanol, followed by water and ether extracts. Sarıkurkcu and Tepe (7) stated that the total flavonoid content in Pyracantha in the ethanol extract was higher than the water extract. In the current study, the highest amount of total flavonoid content was detected in hot water extract, followed by the ethanol and ether extract. However, total flavonoid content was found to be higher in the ethanol extract than the diethyl ether extract. The differences in the flavonoid and phenolic contents of the different solvent extracts may be due to the polarity of the solvents used and the chemical structure of the endogenous extractable compounds (24). The polarity of a solvent is determined to be crucial for the total phenolic and flavonoid contents: a solvent with a higher polarity yields higher phenolic and flavonoid contents. Water is a highly polar solvent which can extract a higher diversity of compounds (25). The result in the present study may be related, partially, to the fact that water aids in the diffusion of extractable compounds through plant tissues (26). On the other hand, the high temperatures in the extraction procedure may have enhanced the transition of these substances to the solvent. It is commonly confirmed that numerous biological activities and curative utilities of plants can be recognized based on the antioxidant activity of the phenolic compounds and flavonoids they include (27). The total phenol and flavonoid contents which were determined in the recent study suggested that *Pyracantha coccinea* Roem. fruit had a number of potential health-associated biological properties thanks to its antimicrobial and antioxidant effects.

Antioxidants work by chelating metals, scavenging a number of free radical species produced in oxidative reactions, and inhibiting free radical formation through reduction of precursors (5). DPPH is a free radical compound that is widely used to assess the free radical scavenging ability of diverse samples because of its easy use, stability (in radical form) and reproducibility. DPPH test is utilized to assess the capacity of antioxidants to scavenge free radicals, which are recognized to be an important factor in biological injury triggered by oxidative stress (3). Similarly, $ABTS^{\bullet+}$ scavenging test is a great assay for assessing the antioxidant activity of chain breaking and hydrogen donating antioxidants (28). The number of studies which have been conducted to assess the antioxidant and general properties of *Pyracantha coccinea* Roem. fruit is quite limited. In a study on the radical scavenging potential of *Pyracantha coccinea* extracts prepared with water, ethanol, acetone, methanol, and diethyl ether, Keser (23) determined that methanol, ethanol, and acetone extracts displayed DPPH and ABTS radical scavenging activity. He suggests that *Pyracantha coccinea* can be an important source of natural antioxidants because of the existence of phenolic compounds (23). In another study, Yoshimura stated that DPPH radical scavenging activity of *Pyracantha coccinea* might arise from the therapeutically effective flavonoid glycosides and other polyphenols it contained (29). In the current investigation, the antioxidant capacities of the extracts which were acquired through various solvents were determined by ABTS and DPPH methods, which expressed scavenging of free radicals (30). DPPH radical scavenging effect was the highest in hot water extract and subsequently in ethanol, while the lowest effect was found in the ether extract. On the other hand, the highest ABTS radical scavenging effect was found in the hot water extract followed by the ethanol extract, while the lowest effect was found in the ether extract. However, DPPH and ABTS activities were found to be higher in the ethanol extract than the diethyl ether extract. Considering the data, hot water and then ethanol solvents appeared to have a good capacity to extract antioxidant molecules because *Pyracantha coccinea* Roem. fruit extracts exhibited varying degrees of antioxidant activity with the potential to act as free radical scavengers. On the other hand, it meaned that the phenolic and flavonoid components which were found to be high in the extraction with hot water exhibited a distinguishable effect on the free radical scavenging.

Most minerals contribute significantly to normal growth, even at threshold levels, and play an important role in biochemical functions, particularly essential enzyme systems, but they can be toxic and pose a health risk at high levels (31). Although the effectiveness of medicinal plants is mainly associated with their components, it has been stated that they may cause health problems due to the heavy metals they may contain if taken for a long-term (32). Therefore, it is very essential to define the levels of these compounds in popular, common, and extensively used herbs (31). To date, there are no reports on the mineral content of *Pyracantha coccinea* Roem. fruit. In the present study, Cr, Co, Ni, and Cu amounts were determined above normal limits, while other metal concentrations were within safety limits. On the other hand, Cd was below detection limits. Co is an important element that is essential for the production of vitamin cobalamin. Although it effects several functions in the human body such as the formation of amino acids and neurotransmitters, excessive Co accumulation in the body induces asthma, fibrosis in the lungs, and high erythrocyte production. Similarly, while Cu is a vital element for the proper functioning of organs and systems in the body, it can be toxic even in slightly high levels. On the other hand, the biochemical function of Ni in animals and humans is still not fully known (33). As one of the trace metal nutrients necessary for humans and animals, the main role of Cr is to help maintain normal glucose tolerance in the body. On the other hand, the maximum intake limit has not been determined as no toxic effect of Cr is known (31). Cd is an element which is not required by humans or plants and can easily cause toxic effects in

humans at low amounts (6). Therefore, the fact that no Cd that was detected in *Pyracantha coccinea* Roem. fruit in the present study was a highly desirable result. However, heavy metals are among the most important pollutants in the environment. Phytoremediation is recently utilized as an environmentally friendly and potentially cost-effective technology used to clean contamination from soil, sediment, and water (34). *Pyracantha coccinea* Roem. fruits used in the present study were collected from a region in the immediate vicinity of a highway. Therefore, some heavy metals (Co, Cr, Cu, and Ni) might be found to be high. Since some of the heavy metals in this study had high levels, it could be suggested that *Pyracantha coccinea* Roem. fruit could be used to remove heavy metals from the soil using its ability to absorb metals necessary for plant growth.

Plants commit a natural source of antimicrobial substances. It has been stated that the antimicrobial activity of plants is associated with the defense mechanism against microorganisms (19). However, the increased resistance of bacteria to common antimicrobial agents and the unwanted side effects of synthetic antimicrobial agents have led medical researchers to subject their attention to the possible antimicrobial properties of herbs. In addition, the antibacterial effects of several medicinal herbs are being investigated because of toxicological concerns related with synthetic preservatives and antioxidants (35). As a result of the literature review, there were only two studies which investigated the antimicrobial effects of *Pyracantha coccinea* Roem. In the study conducted by Turker et al. (36), antimicrobial activity could not be determined on *Staphylococcus aureus* in the extracts prepared by *Pyracantha coccinea* Roem. with cold water, and hot water and cold ethanol. They determined an inhibitory effect of the extract prepared with hot ethanol on *Staphylococcus aureus* (36). It was determined by Turu et al. (37) that *Pyracantha coccinea* Roem. extract which was prepared with ethanol and applied in different doses had antimicrobial effects against *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Candida albicans.* In their study, antimicrobial activity was determined for *Pyracantha coccinea* extracts against *Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus cereus,* and *Candida albicans.* According to the results of the present study, *Pyracantha coccinea* Roem. exhibited antimicrobial activity only against *Bacillus cereus* and *Pseudomonas aeruginosa*. The current study has differences (37) as well as consistency with other studies (36,37). Contrary to the present study, Turu et al. (37) found that *Pyracantha coccinea* Roem. fruit extracts displayed antimicrobial activity against *Staphylococcus aureus* and *Candida albicans*. This difference may have stemmed from the extract preparation method and the applied extract dosage. On the other hand, the application of *Pyracantha coccinea* Roem. fruit extracts which were prepared with different solvents against *Bacillus cereus* did not make a difference in antimicrobial activity based on the statistical data. However, it was determined that the antimicrobial effect of the extract prepared with water in *Pseudomonas aeruginosa* was higher than the other two extracts. The detected antimicrobial activity suggests that these extracts contain compounds that can inhibit the growth of microorganisms. Secondary compounds found in plants may play a role in the defense of plants through cytotoxicity against pathogenic microorganisms, and it may prove their usefulness as antimicrobial drugs for humans (38). In addition, flavonoids (low mass polyphenolic compounds) have antibacterial, antiviral, antifungal, antitumor, antiproliferative, and anti-inflammatory properties (4). It can be said that the antimicrobial effects reported in the present study may have arisen from the contribution of phenolic and flavonoid compounds. However, the fact that *Pyracantha coccinea* Roem. fruit extracts do not show inhibition on *Staphylococcus aureus* and *Candida albicans* suggests that they can be used as a narrow spectrum antimicrobial. However, the cell membrane, cytoplasm, metabolism, and structural functions of the cell of microorganisms are negatively effected by some meatal ions (39). The analyses in the present study show that some heavy metals have high amounts and may have caused antimicrobial effects against *Bacillus cereus* and *Pseudomonas aeruginosa.*

Study Limitations

The main limitation of the present study was that there was no analysis to detect which flavonoid and phenolic compounds in the extracts.

Conclusion

People have recently turned their attention to using natural alternatives such as plant extracts to solve health and environmental problems (19). The current investigation displays the extraction of *Pyracantha coccinea* Roem. fruit via different solvents. Among the studied solvents, water was proved to be the finest for extracting bioactive compounds from *Pyracantha coccinea* Roem. fruit since it resulted in the highest total content of phenolic and flavonoid. Compared with other extracts, the water extract of *Pyracantha coccinea* Roem. fruit showed the highest antimicrobial and antioxidant activity. These findings propose that water is the finest solvent for the extraction of bioactive compounds from *Pyracantha coccinea* Roem. fruit and that the water extract is a promising antimicrobial and antioxidant agent for further drug development. Therefore, the extracts of *Pyracantha coccinea* Roem. fruit could be novel resources to improve new plant based cures for the management of illnesses. *Pyracantha coccinea* Roem. fruit may be a good candidate for further investigations on its usefulness in disorders caused by oxidative stress due to its phenolic and flavonoid contents and antioxidant activity. Additional discoveries are required to break down and purify the extract to discover molecules liable for the detected antioxidant and antimicrobial activity.

Ethics

Ethics Committee Approval: Was not obtained as no animals or humans were used in the study.

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References

1. Hwang KA, Hwang YJ, Song J. Antioxidant activities and oxidative stress inhibitory effects of ethanol extracts from Cornus officinalis on raw 264.7 cells. BMC Complement Altern Med 2016;16:196.
2. Kaneria M, Baravalia Y, Vaghasiya Y, Chanda S. Determination of antibacterial and antioxidant potential of some medicinal plants from saurashtra region, India. Indian J Pharm Sci 2009;71:406-12.
3. Fawole FJ, Sahu NP, Pal AK, Lakra WS. Evaluation of antioxidant and antimicrobial properties of selected Indian medicinal plants. Int J Med Arom Plants 2013;3:69-77.
4. Popoviciu DR, Negreanu-Pirjol T, Motelica L, Negreanu-Pirjol BS. Carotenoids, flavonoids, total phenolic compounds content and antioxidant activity of indigenous *Pyracantha coccinea* M. Roem. Fruits. Rev Chim 2020;71:258-66.
5. Subba B, Basnet P. Antimicrobial and antioxidant activity of some indigenous plants of Nepal. J Pharmacogn Phytochem 2014;3:62-7.
6. Stanojkovic-Sebic A, Pivic R, Josic D, Dinic Z, Stanojkovic A. Heavy metals content in selected medicinal plants commonly used as components for herbal formulations. JAS 2015;21:317-25.
7. Sarikurkcu C, Tepe B. Biological activity and phytochemistry of firethorn (*Pyracantha coccinea* M.J. Roemer). J Funct Foods 2015;19:669-75.
8. Davis PH. Chamberlain DF, Victoria A. Matthews. Flora of Turkey and the East Aegean Islands, Volume 4. Editor P. H. DAVIS, vol. 4, Edinburgh University Press, 1972. JSTOR, http://www.jstor.org/stable/10.3366/j.ctvxcrc36. Accessed 18 Jan. 2023.
9. Güner A. Checklist of Turkish flora (vascular plants). Nezahat Gökyiğit Botanical Garden and Flora Research Association Publication, İstanbul; 2012.
10. Spanos GA, Wrolstad RE. Influence of processing and storage on the phenolic composition of thompson seedless grape juice. J Agric Food Chem 1990;38:1565-71.
11. Dewanto V, Wu X, Adom KK, Liu RH. Thermal processing enhances the nutritional value of tomatoes by increasing total antioxidant activity. J Agric Food Chem 2002;50:3010-4.
12. Brand-Williams W, Cuvelier ME, Berset C. Use of a free radical method to evaluate antioxidant activity. Lebensm Wiss Technol 1995;28:25-30.
13. Re R, Pellegrini N, Proteggente A, Pannala A, Yang M, Rice-Evans C. Antioxidant activity applying an improved ABTS radical cation decolorization assay. Free Radic Biol Med 1999;26:1231-7.
14. Hajar EWI, Ziad A, Sulaiman B, Sakinah AMM. Assessment of heavy metals tolerance in leaves, stems and flowers of Stevia rebaudiana plant. Procedia Environ Sci 2017;20:386-93.
15. Bhalodia NR, Shukla VJ. Antibacterial and antifungal activities from leaf extracts of Cassia fistula l.: An ethnomedicinal plant. J Adv Pharm Technol Res 2011;2:104-9.
16. Nisha MC, Subramanian MS, Prathyusha P, Santhanakrishnan R. Comparative studies on antimicrobial activity of Artemisia sieversiana Ehrhart. Ex. Willd. and Origanum vulgare L. Int J Pharmtech Res 2010;2:1124-7.
17. Daoud A, Malika D, Bakari S, Hfaiedh N, Mnafgui K, Kadri A, et al. Assessment of polyphenol composition, antioxidant and antimicrobial properties of various extracts of date palm pollen (DPP) from two tunisian cultivars. Arab J Chem 2019;12:3075-86.
18. Baba SA, Malik SA. Evaluation of antioxidant and antibacterial activity of methanolic extracts of Gentiana kurroo royle. Saudi J Biol Sci 2014;21:493-8.
19. Reyes-Munguía A, Carrillo-Inungaray ML, Carranza-Álvarez C, Pimentel-González DJ, Alvarado-Sánchez B. Antioxidant activity, antimicrobial and effects in the immune system of plants and fruits extracts. Front Life Sci 2016;9:90-8.
20. Nawaz H, Shad MA, Rehman N, Andaleeb H, Ullah N. Effect of solvent polarity on extraction yield and antioxidant properties of phytochemicals from bean (Phaseolus vulgaris) seeds. Braz J Pharm Sci 2020;56:e17129.
21. Saeed N, Khan MR, Shabbir M. Antioxidant activity, total phenolic and total flavonoid contents of whole plant extracts Torilis leptophylla L. BMC Complement Altern Med 2012;12:221.
22. Sen S, De B, Devanna N, Chakraborty R. Total phenolic, total flavonoid content, and antioxidant capacity of the leaves of Meyna spinosa Roxb, an Indian medicinal plant. Chin J Nat Med 2013;11:149-57.
23. Keser S. Antiradical activities and phytochemical compounds of firethorn (*Pyracantha coccinea*) fruit extracts. Nat Prod Res 2014;28:1789-94.
24. Sajid ZI, Anwar F, Shabir G, Rasul G, Alkharfy KM, Gilani AH. Antioxidant, antimicrobial properties and phenolics of different solvent extracts from bark, leaves and seeds of Pongamia pinnata (L) Pierre. Molecules 2012;17:3917-32.
25. Li H, Zhang D, Tan LH, Yu B, Zhao SP, Cao WG. Comparison of the antioxidant properties of various solvent extracts from Dipsacus asperoides and identification of phenolic compounds by LC-ESI-QTOF-MS–MS. S Afr J Bot 2017;109:1-8.
26. Borges A, José H, Homem V, Simões M. Comparison of techniques and solvents on the antimicrobial and antioxidant potential of extracts from Acacia dealbata and Olea europaea. Antibiotics (Basel) 2020;9:48.
27. Jing L, Ma H, Fan P, Gao R, Jia Z. Antioxidant potential, total phenolic and total flavonoid contents of Rhododendron anthopogonoides and its protective effect on hypoxia-induced injury in PC12 cells. BMC Complement Altern Med 2015;15:287.
28. Hameed S, Imran A, Nisa M, Arshad MS, Saeed F, Arshad MU, et al. Characterization of extracted phenolics from black cumin (Nigella sativa linn), coriander seed (Coriandrum sativum L), and fenugreek seed (Trigonella foenum-graecum). Int J Food Prop 2019;22:714-26.
29. Yoshimura M. Structure elucidation of antioxidative polyphenols and their biological properties. J Pharm Soc Jpn 2014;134:957-64.
30. Acet T, Özcan K. Determination of antioxidant and antimicrobial properties of Lady's Mantle (Alchemilla ellenbergiana) extracts. GÜFBED/GUSTIJ 2018;8:113-21.
31. Bhat R, Kiran K, Arun AB, Karim AA. Determination of mineral composition and heavy metal content of some nutraceutically valued plant products. Food Anal Methods 2010;3:181-7.

32. Kostić D, Mitić S, Zarubica A, Mitić M, Veličković J, Randjelović S. Content of trace metals in medicinal plants and their extracts. Hem Ind 2011;65:165-70.

33. Fagbohun OF, Babalola OO, Agboola FK, Joseph JS, Malindisa S, Msagati TAM. Evaluation of phytochemicals, antioxidants, trace elements in Kigelia Africana fruit extracts and chemical profiling analysis using UHPLC-qTOF-MS2 spectrometry. Biol Trace Elem Res 2020;195:679-95.

34. Tangahu BV, Abdullah SRS, Basri H, Idris M, Anuar N, Mukhlisin M. A Review on heavy metals (As, Pb, and Hg) uptake by plants through phytoremediation. Int J Chem Eng 2011;1-31.

35. Mahboubi A, Asgarpanah J, Sadaghiyani PN, Faizi M. Total phenolic and flavonoid content and antibacterial activity of Punica granatum L. var. pleniflora flowers (Golnar) against bacterial strains causing foodborne diseases. BMC Complement Altern Med 2015;15:366.

36. Turker AU, Yıldırım AB, Karakas FP. Antibacterial and antitumor activities of some wild fruits grown in Turkey. Biotechnol Biotechnol Equip 2012;26:2765-72.

37. Turu D, Bozyel ME, Candan K, Yakan MA, Benek A, Canlı K. In vitro antimicrobial and antioxidant activities of *Pyracantha coccinea* fruits ethanol extract. Int Multidiscip Res J 2020;4:89-93.

38. Abeysinghe PD, Chaminda DSW. Screening of petroleum ether, chloroform, ethyl acetate, ethanol and water extracts of medicinal plant, Avicennia marina for antibacterial activity against antibiotic resistant bacteria species, Staphylococcus and Proteus. J Pharm Biomed Sci 2011;11:1-4.

39. Chakraborty J, Das S. Characterization and cadmium-resistant gene expressionof biofilm-forming marine bacterium Pseudomonas aeruginosa JP-11. Environ Sci Pollut Res 2014:14:1356-308.

Original Article

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Evaluation of Musculoskeletal Disorders and the Effect of Ergonomic Conditions in Karadeniz Technical University Students Receiving Distance Education Due to COVID-19

COVID-19 Nedeniyle Uzaktan Eğitim Alan Karadeniz Teknik Üniversitesi Öğrencilerinde Kas İskelet Sistemi Rahatsızlıkları ve Ergonomik Koşulların Etkisinin Değerlendirilmesi

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ABSTRACT

Objective: The aim of the study was to evaluate the effects of musculoskeletal disorders (MSDs) and ergonomic conditions in Karadeniz Technical University students who received distance education due to coronavirus disease-2019 (COVID-19).

Methods: The population of this descriptive study consisted of 33,219 students at Karadeniz Technical University. Three hundred two university students selected using the convenience sampling method were included in the study by completing the questionnaire completely. Participation in the research was based on volunteering. The questionnaire consisted of sociodemographic and personal characteristics, online education and work environment characteristics, Cornell Musculoskeletal Disorders Questionnaire and International Physical Activity Questionnaire Short Form.

Results: The mean of participants' Total Cornell Score was 76.6±97.3 (0-624). The chairs used by 205 (67.9%) of the participants during the lesson did not have wheels and 360° rotation feature. Total Cornell Score of the participants without head-neck and lumbar support was statistically significantly higher than those with head-neck and lumbar support (p values were 0.009 and 0.006, respectively). The Total Cornell Score was statistically significantly higher in the participants who could not put their feet on the ground completely while sitting on the chair compared to the participants who could keep their feet on the ground completely (p=0.018). The Total Cornell Score was statistically significantly lower in those who

ÖZ

Amaç: Çalışmanın amacı, koronavirüs hastalığı-2019 (COVID-19) nedeniyle uzaktan eğitim alan Karadeniz Teknik Üniversitesi öğrencilerinde kas-iskelet sistemi rahatsızlıklarının ve ergonomik koşulların etkilerini değerlendirmektir.

Yöntemler: Tanımlayıcı tipteki bu araştırmanın evrenini Karadeniz Teknik Üniversitesi'nde eğitimine devam eden 33.219 öğrenci oluşturmaktadır. Kolayda örnekleme yöntemiyle seçilen 302 üniversite öğrencisi anketi eksiksiz doldurarak çalışmaya dahil edilmiştir. Araştırmaya katılım gönüllülük esasına dayanmaktadır. Anket, sosyodemografik ve kişisel özellikler, çevrimiçi eğitim ve çalışma ortamı özellikleri, Cornell Kas-iskelet Sistemi Rahatsızlıkları Anketi ve Uluslararası Fiziksel Aktivite Anketi Kısa Formu'ndan oluşmaktadır.

Bulgular: Katılımcıların Toplam Cornell Puanı ortalaması 76,6±97,3 (0-624) idi. Katılımcıların 205'inin (%67,9) ders sırasında kullandığı sandalyenin tekerlek ve 360° dönebilme özelliği yoktu. Baş-boyun ve bel desteği olmayan katılımcıların Toplam Cornell Skoru, baş-boyun ve bel desteği olanlara göre daha yüksek ve istatistiksel olarak anlamlı idi (p değerleri sırasıyla 0,009 ve 0,006). Sandalyede otururken ayağını tam olarak yere basamayan katılımcıların Toplam Cornell Skoru, ayaklarını tamamen yere basabilen katılımcılara göre daha yüksek ve istatistiksel olarak anlamlı idi (p=0,018). Ders sırasında kullanılan odanın aydınlatması yeterli olanlarda olmayanlara göre Toplam Cornell Skoru daha düşük ve

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had adequate lighting in the room used during the lesson than those who did not have (p=0.028).

Conclusion: This study showed the importance of providing ergonomically appropriate conditions in the working environment in order to prevent musculoskeletal disorders.

Keywords: Ergonomics, musculoskeletal disorders, COVID-19, distance education, online learning

istatistiksel olarak anlamlı bulunmuştur (p=0,028).

Sonuç: Bu çalışma, kas iskelet sistemi rahatsızlıklarını önlemek için çalışma ortamında ergonomik olarak uygun koşulların sağlanmasının önemini göstermiştir.

Anahtar Sözcükler: Ergonomi, kas-iskelet sistemi rahatsızlıkları, COVID-19, uzaktan eğitim, çevrimiçi öğrenim

Introduction

Musculoskeletal disorders (MSDs) are defined as conditions that can occur as a result of single trauma such as fractures, sprains and strains or cumulative trauma such as nerve compression disorders (carpal tunnel syndrome etc.), osteoarthritis and rheumatoid arthritis. They cover a wide range of inflammatory and degenerative conditions affecting muscles, ligaments, tendons, nerves, bones and joints (1). They are characterized by pain (usually permanent) and limitations in mobility, dexterity, and general functioning which causes varying degrees of deterioration in the quality of life of individuals (2).

The MSD is among the leading causes of morbidity all over the world. The 2019 analysis of Global Burden of Disease data showed that approximately 1.71 billion people worldwide had MSD (2). Low back pain and other musculoskeletal conditions are among the 10 causes with the largest absolute increases in Disability Adjusted Life Years (DALY) between 1990 and 2019 and are common from young to older age. In addition, between 1990 and 2019, an increase by 30.7% was found in age-standardized DALY for other MSDs (3). According to the data of the "National Burden of Disease Study"conducted in Turkey in 2013, the burden of disease due to low back and neck pain among non-communicable diseases increased by 37% between 2000 and 2013 (4).

Repetitive situations such as keyboard and mouse use, static position and wrong body posture may cause MSDs in computer users (5). Although working in a sitting position does not require much physical effort, working in long-term and inappropriate body postures can lead to MSDs. (6). Many studies involving office workers using computers have shown that prolonged sitting and computer use cause MSDs and exacerbate existing problems. Madhwani and Kishare. (7) reported that employees with 4-7.5 hours of sitting time had significantly more MSD symptoms than those who worked 2-4 hours.

In addition, the physical conditions of the working environment and the ergonomic inappropriateness of the tables, chairs and other equipment used can lead to the formation of MSD. Korhonen et al. (8) reported that physical characteristics such as the lighting, temperature and size of the working environment were associated with neck pain. In a systematic review by van Niekerk et al. (9), it was shown that ergonomic chair intervention with adjustable features reduced MSDs in desk workers.

The daily habits, working and educational conditions of millions of people have changed drastically due to the measures taken within the scope of combating the coronavirus disease 2019 (COVID-19) pandemic. The distance education process has started in schools all over the world in different forms and levels. With the decision taken by the Council of Higher Education in our country, universities have started distance education within their capacity as of March 23, 2020 (10). In a study examining the risk factors of MSD related to ergonomic conditions and working style in distance education students, Edwar et al. (11) reported that limited workplace support and working posture were effective on MSD. Karingada and Sony. (12) stated that approximately 80% of the students experienced some MSD symptoms in the head, neck and eyes since they started online learning.

In this study, it was aimed to evaluate the effects of MSDs and ergonomic conditions in Karadeniz Technical University students who received distance education due to COVID-19.

Methods

Research Population

The population of this descriptive study consisted of 33,219 students continuing their education at Karadeniz Technical University. Students continued their education by distance education from March 23, 2020 until July 18, 2021. This process took approximately 16 months. Participants to be included in the study were selected using convenience sampling method. In this study, whichwas based on volunteerism, the question "Do you want to participate in the study?" was asked at the beginning of the questionnaire. Three hundred two university students who volunteered to participate in the study by answering "yes" and completed the form completely were included in the study.

Data Collection

A survey form developed by the researchers was used as a data collection tool. This form was converted into an online survey form via SurveyMonkey. The link of the online survey form was sent to the e-mail addresses of the students registered in the system via Karadeniz Technical University Data Processing Center. Reminders were made via e-mail addresses 15 days after the questionnaire was sent. Data collection was carried out between 31.05.2021 and 18.07.2021.

The questionnaire form used in the research consisted of 4 parts.

Sociodemographic and personal characteristics: In this section, gender, age, school and class of education, height, weight, smoking and chronic disease status, refractive errors in the eyes and use of glasses/lenses were questioned.

Online education and working environment features: The average daily online course duration, the place where the lecture is attended, the technological device used to listen to the lecture, and the use of an external keyboard were questioned. It was questioned whether the lighting of the room and size of the desk and chair used to attend the lesson were appropriate for studying. The chair used during the lesson was questioned in terms of existence of wheels, 360-degree rotation, height adjustment, adjustment of back inclination, lumbar support, head and neck support, and presence of armrest.

Cornell musculoskeletal disorders questionnaire: It was developed at Cornell University to evaluate MSD (13). Turkish validity and reliability study was performed by Erdinç et al. (14) in 2008. It evaluates the frequency and severity of pain, aches or discomfort in 11 different body parts in the last 7 days and whether it interferes with ability to work. The answers for the frequency of feeling pain are "never, 1-2 times a week, 3-4 times a week, at least once a day, many times a day" and they are scored as 0, 1.5, 3.5, 5 and 10, respectively. The options for pain intensity are "mild, severe, very severe" and hindrance to work is evaluated by multiplying the answers "not at all, a bit of a hindrance, a lot of hindrance" by 1, 2, 3, respectively. The Total Cornell Score, which shows the MSDs, is calculated by adding the scores calculated separately for each region. The Total Cornell Score is scored between 0-1620, and as the score increases, the frequency and severity of MSD and the state of being prevented from doing work increases.

International Physical Activity Questionnaire Short Form: It was developed by Craig et al. (15)but diverse physical activity measures in use prevent international comparisons. The International Physical Activity Questionnaire (IPAQ in 2003 to determine the level of physical activity. Turkish validity and reliability studies were performed by Öztürk (16) in 2005. The questionnaire includes questions about physical activity performed for at least 10 minutes in the last 7 days. Information is provided on how many days in the last 7 days, and for how long per day, vigorous activities, moderate-intensity activities and walking have been done. In the last question, the time spent sitting without moving daily in the last 7 days is questioned in minutes. The MET method is used to determine the level of physical activity. The standard MET values for these activities were determined by Craig et al. as 3.3, 4.0 and 8.0 for walking, moderate-intensity activity, and vigorous activity, respectively. A score is obtained as "MET minutes/week" by multiplying the minute, day and MET value (multiples of resting oxygen consumption). The total activity score is obtained by adding the walking score (3.3 * walking time * number of days walked), moderate activity score (4.0 *duration of moderate-intensity activity * days of moderate-intensity activity) and vigorous activity score (8.0 * duration of vigorous activity * number of days of vigorous activity). According to the total activity score, the physical activity level is inactive if <600 MET-minutes/week, minimally active if 600-3,000 MET-minutes/week and very active level if >3,000 MET-minutes/week.

Statistic Analysis

Body mass index (BMI) was calculated using the height and weight of the participants. According to the World Health Organization criteria, BMI is classified as <18.5, 18.5-24.9, 25.0-29.9, >30.0 respectively, as underweight, normal weight, overweight and obese (17). The IBM Statistics for Windows SPSS 22.0 statistical package program (SPSS) was used in the analysis of the data. Descriptive statistics; numbers and percentages are given for categorical variables, mean, standard deviation (SD), minimum and maximum values are given for numerical variables. The conformity of the data to the normal distribution was evaluated by visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov or Shapiro-Wilk tests) methods. Mann Whitney U or Kruskal Wallis Analysis of Variance was used in the analysis of the measurement data. In all statistical analyses, the significance value was accepted as $p<0.05$.

Permissions for the Study

Permission for the research was obtained from the Ethics Committee of Karadeniz Technical University Faculty of Medicine (dated 21.04.2021 and numbered 24237859-378) and the Rectorate of Karadeniz Technical University (dated 10.03.2021 and numbered 44710342-929-12694).

Results

The mean of the participants' Total Cornell Score ± SD was calculated as 76.6±97.3 (0-624). The mean age of the participants was 22.0±3.2 (18.0-53.0), 141 (46.7%) of them were women. Total Cornell Score of women was significantly higher than men ($p<0.001$). The sociodemographic and personal characteristics of the participants affecting the Total Cornell Score are presented in Table 1.

Of the participants, 63 had chronic disease. Chronic diseases of the participants were;

MDS in 19 (30.2%), respiratory system diseases in 11 (17.5%), psychiatric diseases in 9 (14.3%), endocrine diseases in 6 (9.5%), digestive system diseases in 6 (9.5%), migraine in 5 (7.9%), kidney diseases in 4 (6.3%), allergic diseases in 3 (4.8%), immune system diseases in 3 (4.8%), cardiovascular system diseases in 2 (3.2%) and dermatological diseases in 2 (3,2%). The daily lesson duration of the participants on average was 3.4±2.3 (0.3-12) hours. There was no significant difference between the daily lesson time and the Total Cornel Score. Distance education and working environment characteristics affecting the Total Cornell Score of the participants are presented in Table 2.

The chairs used by 205 (67.9%) of the participants during the lesson did not have wheels and the Total Cornell Score of the participants who did not use a chair with wheel was found to be higher than those who used it ($p=0.046$). The features of the chairs used during the lesson that affect the Total Cornell Score are presented in Table 3.

Discussion

The COVID-19 pandemic has caused many changes in lifestyles. As a result of the measures implemented, the education of the students continued in the form of distance education. Therefore, as a result of not providing ergonomic conditions at home, students have a risk of developing MSD.

Total Cornell Score in women was statistically higher than men. Woo et al. (18) showed that women reported more upper extremity MSD than men. This difference can be explained by the lower body size or muscle mass in women. In addition, the fact that women were more willing to report or seek medical help for pain or discomfort may have affected this result (19,20).

Total Cornell Score of participants with normal BMI was found to be statistically significantly higher than overweight/obese participants. Evaluations made with BMI do not provide detailed information about body composition, such as body fat percentage and lean body mass (21). BMI could be calculated as higher than 24.9 in people with more muscle mass. For this reason, the Total Cornell Score may have been found to be lower in those who were overweight/obese according to BMI, since their muscle mass was higher.

Many studies show that sitting for a long time causes MSD. However, in our study, no significant difference was found

Table 1. Sociodemographic and personal characteristics of the participants affecting the Total Cornell Score (n=302)

Features	Mean ± SD	Min.-max.	Total Cornell Score		
			Median	**Min.-max.**	**p value**
Age	22.0 ± 3.2	18.0-53.0			
≤21 years old			51.0	0-624.0	0.077
>21 years old			34.5	0-454.5	
Gender	**n**	**%**			
Female	141	46.7	62.0	0-522.0	**<0.001**
Male	161	53.3	26.5	0-624.0	
BMI	**n**	**%**			
Underweight	21	7.0	51.0	3.0-280.0	**0.029**
Normal weight	188	62.3	52.0[a]	0-624.0	
Overweight	65	21.5	30.5[b]	0-258.0	
Obese	28	9.3			
Smoking	**n**	**%**			
Yes	66	21.9	53.0	0-624.0	0.370
No	199	65.9	45.5	0-522.0	
Quitted	37	12.3			
	Mean ± SD	**Min.-max.**			
Pack year of cigarettes (n=66)	3.4 ± 3.7	0-18.0			
≤2 packs/year			82.0	1.5-462.0	0.110
>2 packs/year			43.7	0-624.0	
Chronic disease status	**n**	**%**			
Yes	63	20.9	62.0	0-522.0	0.051
No	239	79.1	43.5	0-624.0	
Eye refractive error	**n**	**%**			
Yes	131	43.4	47.0	0-522.0	0.585
No	171	56.6	47.0	0-624.0	
Use of glasses/lenses (n=131)	**n**	**%**			
Yes	116	88.5	47.0	0-522.0	0.942
No	15	11.5	49.0	0-434.0	
Physical activity level	**n**	%			
Inactive	122	40.4	47.2	0-624.0	0.859
Minimally active	112	37.1	42.5	0-522.0	
Very active	68	22.5	49.5	0-447.5	

[a,b]Significant difference was found between different letters,
SD: Standard deviation, Min: Minimum, max: Maximum

Table 2. Distance education and working environment characteristics that affect the Total Cornell Score of the participants

Features	Mean ± SD	Min.-max.	Total Cornell Score		
			Median	Min.-max.	p value
Daily lesson duration (hours)	3.4 ± 2.3	0.3-12.0			
≤3 hours			45.5	0-624.0	0.941
>3 hours			49.0	0-522.0	
Duration of a lesson	38.0±27.5	0-180.0			
≤40 minutes			47.0	0-522.0	0.858
>40 minutes			47.0	0-624.0	
Location when attending lectures	**n**	**%**			
Study desk	235	77.8	43.5	0-522.0	0.353
Sofa-armchair	29	9.6	51.0	0-624.0	
Dinner table	20	6.6			
Bed	18	6.0			
Technological product mostly used while joining lectures					
Laptop	235	77.8	47.0	0-522.0	0.489
Mobile phone	32	10.6	50.7	0-624.0	
Desktop computer	29	9.6	39.0	0-274.5	
Tablet	6	2.0	17.0	4.5-624.0	
Using an external keyboard					
Yes	79	26.2	29.0	0-454.5	**0.024**
No	223	73.8	51.5	0-624.0	
Phone/tablet holder use (n=38)*					
Yes	10	26.3	66.0	0-450.0	0.497
No	28	73.7	45.7	0-624.0	
Evaluation of the physical environment used while studying by the participants					
Comfort of the desk					
Yes	132	43.7	33.2[a]	0-522.0	**<0.001**
Partially	109	36.1	52.0[b]	0-462.0	
No	61	20.2	56.5[b]	0-624.0	
Comfort of the chair					
Yes	88	29.1	32.5[a]	0-522.0	**0.007**
Partially	107	35.4	47.0[b]	0-462.0	
No	107	35.4	51.0[b]	0-624.0	
Suitability of room lighting					
Yes	180	59.6	43.2[a]	0-522.0	**0.028**
Partially	77	25.5	49.0	0-462.0	
No	45	14.9	70.0[b]	0-624.0	
Reflection on the screen of the technological device					
Yes	72	23.8	51.5	0-624.0	0.131
Partially	63	20.9	52.0	0-434.0	
No	167	55.3	43.5	0-522.0	
Adequacy of room size					
Yes	207	68.5	42.5[a]	0-522.0	**0.015**
Partially	56	18.5	69.3[b]	0-447.5	
No	39	12.9	74.5[b]	0-624.0	

*Participants who mostly use phones or tablets answered.
[a,b]Significant difference was found between different letters.
SD: Standard deviation, Min: Minimum, max: Maximum

between the daily lesson time and the Total Cornell Score. In a study conducted by Karingada and Sony (12) on university students, daily online learning hours of students were found to be positively correlated with MSD symptoms in some body regions.

The Total Cornell Score was found to be statistically lower in those whose room used during the lesson was adequately lit than in those whose room was not adequately lit, and in those whose room size was sufficient compared to those whose room was partially adequate or not. D'Errico et al. (22) reported

Table 3. The features of the chair used during the lesson that affect the Total Cornell Score

Features	n	%	Total Cornell Score		
			Median	Min.-max.	p value
Wheel presence					
Yes	97	32.1	37.0	0-454.5	**0.046**
No	205	67.9	49.0	0-624.0	
Number of wheels (n=97)	**Mean ± SD**	**Min.-max.**			
	4.8 ± 0.7	3.0-6.0			
Ergonomically suitable (5 wheels)			30.5	0-454.5	0.211
Ergonomically unsuitable			53.0	0-366.0	
360° rotation	**n**	**%**			
Yes	97	32.1	35.0	0-454.5	**0.045**
No	205	67.9	49.0	0-624.0	
Height adjustable					
Yes	98	32.5	38.0	0-454.5	0.081
No	204	67.5	49.0	0-624.0	
Keeping the feet flat on the floor while sitting in the chair					
Yes	251	83.1	45.5	0-624.0	**0.018**
No	51	16.9	80.0	0-46.0	
The height of the back is high enough to support the head and neck region					
Yes	61	20.2	29.5	0-299.0	**0.029**
No	241	79.8	49.0	0-624.0	
Has head and neck support					
Yes	28	9.3	17.5	0-299.0	**0.009**
No	274	90.7	47.75	0-624.0	
Suitability of the head and neck support for the individual (n=28)					
Yes	24	85.7	12.7	0-299.0	0.066
No	4	14.3	63.7	24.0-280.0	
Having lumbar support					
Yes	109	36.1	33.0	0-522.0	**0.006**
No	193	63.9	51.5	0-624.0	
Suitability of the lumbar support to the individual (n=109)					
Yes	56	51.4	17.7	0-299.0	**0.001**
No	53	48.6	54.0	1.5-522.0	
Adjustable back inclination					
Yes	44	14.6	32.5	0-299.0	**0.045**
No	258	85.4	47.5	0-624.0	
Having arm rest					
Yes	124	41.1	41.5	0-624.0	0.116
No	178	58.9	51.2	0-522.0	
Adjustable armrest (n=124)					
Yes	13	10.5	17.0	0-91.0	0.184
No	111	89.5	43.0	0-624.0	

SD: Standard deviation, Min: Minimum, max: Maximum

that neck and shoulder symptoms were more common in participants with insufficient desk lighting. Insufficient lighting may cause movements that will disrupt body posture, such as approaching and leaning towards the screen in order to provide a better view, and MSD can develop as a result of the repetition of these movements. In the study conducted by Helland et al., more MSD was reported in participants with a small study room size (23). The small size of the room may cause musculoskeletal discomfort by preventing people from using sufficiently large tables, chairs and other equipment and reducing the distance they can move.

Laptops have a compact screen and keyboard. For this reason, when people adjust the screen height in the appropriate position, the keyboard may remain in an ergonomically unsuitable position. In addition, tablets and mobile phones often do not have a keyboard, which can cause fingers to bend while typing. For these reasons, the use of an external keyboard may contribute to the prevention of MSD. In this study, the Total Cornell Score of the participants who did not use an external keyboard was found to be higher than the participants who used it. In the study by Madhwani et al. (24), the use of external keyboard and mouse was found to be associated with MSD.

In a study by Malińska et al. (25), it was stated that the size and shape of the back support, and the use of a chair that would provide a comfortable position, reduced low back and neck pain in women. The Total Cornell Score of the participants whose chair back height was high enough to support the head-neck region and who had head-neck region support was found to be lower. This can be explained by supporting the neck area, preventing the neck from being in an inappropriate position, and reducing the stress on the neck muscles.

Small changes in the chair's back inclination angle significantly affect the load that the upper body must bear. Adjusting the chair back inclination angle can ensure that the upper body, extremities, head and neck are kept in the desired position with less muscle strength requirement (26). The Total Cornell Score of the participants whose chair can rotate 360 degrees and back inclination can be adjusted was found to be lower.

Working chair with ergonomic adjustable features is important in terms of protecting the health of the musculoskeletal system by complying with the anthropometry of the person. While sitting, the intervertebral discs, muscles and ligaments have to bear the load of the lumbar vertebrae. The chair's lumbar support reduces the stress on these structures (27). The Total Cornell Score of the participants who had lumbar support in the chair and thought that the lumbar support was suitable for their body was found to be lower. The Total Cornell Score of the participants who could not touch the ground completely while sitting on the chair was found to be higher than those who could touch it completely. In the study conducted by Kaya Aytutuldu et al. (28), it was stated that approximately 50% of the participants with pain in the lower back, neck and upper extremities did not touch the ground while sitting. The fact that the chair has 5 wheels can help reduce muscle stress by providing balanced and easy movement. Total Cornell Score of the wheelchair users was lower. However, no significant difference was found with the use of an ergonomic 5-wheel chair. In the study conducted by Malińska et al. (25), it was found that the use of a 5-wheel ergonomic chair reduced the risk of neck and low back pain.

Conclusion

In this study, gender, body mass index, use of an external keyboard, the comfort of the desk and chair used during the lesson, the size of the room and the adequacy of the lighting, and the fullness of the feet while sitting in the chair were found to be effective in the formation of musculoskeletal disorder (MSD). In addition, features of the chairs such as being wheeled, having 360 degree rotation, height of the back to support the head and neck region, presence of head, neck and lumbar support, the conformity of the lumbar support to the body and adjustable back inclination were found to be effective in the formation of MSD. However, refractive error in the eye, duration of the daily lesson and physical activity level were not found to be effective in the formation of MSD.

This study showed the importance of providing ergonomically appropriate conditions in the working environment in order to prevent the occurrence of MSD. The use of foot support to ensure that the feet are fully on the ground while sitting and providing head, neck and lumbar support will reduce the risk of MSD. It would be beneficial to use an external keyboard to prevent ergonomically unsuitable postures. It is thought that improving the physical properties of the working environment such as size and lighting will also be effective in preventing the occurrence of MSD.

Ethics

Ethics Committee Approval: Permission for the research was obtained from the Ethics Committee of KTU Faculty of Medicine (dated 21.04.2021 and numbered 24237859-378) and the Rectorate of KTU (dated 10.03.2021 and numbered 44710342-929-12694).

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Authorship Contributions

Concept: Ü.Ö., K.Ş., M.G.Ü., M.T., N.E.B., Design: Ü.Ö., K.Ş., M.G.Ü., M.T., N.E.B., Data Collection or Processing: Ü.Ö., Analysis or Interpretation: Ü.Ö., K.Ş., M.G.Ü., M.T., N.E.B., Literature Search: Ü.Ö., K.Ş., M.G.Ü., Writing: Ü.Ö., K.Ş., M.G.Ü., M.T., N.E.B.

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References

1. Punnett L, Wegman DH. Work-related musculoskeletal disorders: The epidemiologic evidence and the debate. J Electromyogr Kinesiol 2004;14:13-23.
2. WHO. Musculoskeletal conditions [Internet]. 2021. (cited 02.07.2021) Available from: https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions
3. Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204-22.
4. National Burden of Disease Study 2017 [Internet]. 2017. (cited 20.08.2021) Available from: https://tip.hacettepe.edu.tr/ekler/pdf/ulusal_program.pdf
5. Mohammadipour F, Pourranjbar M, Naderi S, Rafie F. Work-related musculoskeletal disorders in Iranian office workers: prevalence and risk factors. J Med Life 2018;11:328-33.
6. Baker R, Coenen P, Howie E, Williamson A, Straker L. The short term musculoskeletal and cognitive effects of prolonged sitting during office computer work. Int J Environ Res Public Health 2018;15:1678.
7. Madhwani, Kishore P PN. Web-based KAP intervention on office ergonomics: a unique technique for prevention of musculoskeletal discomfort in global corporate offices. Indian J Occup Int Med 2017;21:18-22.
8. Korhonen T, Ketola R, Toivonen R, Luukkonen R, Häkkänen M, Viikari-Juntura E. Work related and individual predictors for incident neck pain among office employees working with video display units. Occup Environ Med 2003;60:475-82.
9. van Niekerk SM, Louw QA, Hillier S. The effectiveness of a chair intervention in the workplace to reduce musculoskeletal symptoms. A systematic review. BMC Musculoskelet Disord. 2012;13:145.
10. Durak G, Çankaya S, İzmirli S. Examining the Turkish universities' distance education systems during the COVID-19 pandemic. EDMED 2020;14:787-810.
11. Edwar M, Moch BN, Muslim E. Ergonomics and workstyle risk factors analysis of musculoskeletal disorders in students conducting distance learning. In: ACM International Conference Proceeding Series. Association for Computing Machinery; 2020.
12. Karingada KT, Sony M. Demonstration of the relationship between MSD and online learning during the COVID-19 pandemic. J Appl Res High Educ 2021;14:200-22.
13. Sethi J, Sandhu JS, Imbanathan V. Effect of body mass index on work related musculoskeletal discomfort and occupational stress of computer workers in a developed ergonomic setup. Sport Med Arthrosc Rehabil Ther Technol 2011;3:1-7.
14. Erdinc O, Hot K, Ozkaya M. Turkish version of the Cornell Musculoskeletal Discomfort Questionnaire: cross-cultural adaptation and validation. Work. 2011;39:251-60.
15. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;3:1381-95.
16. Öztürk M. The validity and reliability of the International Physical Activity Questionnaire and determination of physical activity levels in üniversity education students. Master Thesis, Hacettepe University Health Science Institute, Ankara. 2005. Available at: https://toad.halileksi.net/sites/default/files/pdf/uluslararasi-fiziksel-aktivite-anketi
17. WHO. Body mass index - BMI. (cited 1.10.2021) Available from: https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi
18. Woo EHC, White P, Lai CWK. Musculoskeletal impact of the use of various types of electronic devices on university students in Hong Kong: An evaluation by means of self-reported questionnaire. Man Ther 2016;26:47-53.
19. Treaster DE, Burr D. Gender differences in prevalence of upper extremity musculoskeletal disorders. Ergonomics 2004;47:495-526.
20. Collins JD, O'Sullivan LW. Musculoskeletal disorder prevalence and psychosocial risk exposures by age and gender in a cohort of office based employees in two academic institutions. Int J Ind Ergon 2015;46:85-97.
21. Devrim A, Bilgiç P. Is the Use of body mass index sufficient to assess health risks? Bozok Med J 2019;9:144-51.
22. D'Errico A, Caputo P, Falcone U, Fubini L, Gilardi L, Mamo C, et al. Risk factors for upper extremity musculoskeletal symptoms among call center employees. J Occup Health 2010;52:115-24.
23. Helland M, Horgen G, Kvikstad TM, Garthus T, Aarås A. Will musculoskeletal and visual stress change when visual display unit (VDU) operators move from small offices to an ergonomically optimized office landscape? Appl Ergon 2011;42:839-45.
24. Madhwani KP, PK Nag. Web-based kap intervention on office ergonomics: a unique technique for prevention of musculoskeletal discomfort in global corporate offices. Indian J Occup Env Med 2017;21:18-22.
25. Malińska M, Bugajska J, Bartuzi P. Occupational and non-occupational risk factors for neck and lower back pain among computer workers: a cross-sectional study. Int J Occup Saf Ergon 2021;27:1108-15.
26. Rohlmann A, Zander T, Graichen F, Dreischarf M, Bergmann G. Measured loads on a vertebral body replacement during sitting. Spine J 2011;11:870-5.
27. Mörl F, Bradl I. Lumbar posture and muscular activity while sitting during office work. J Electromyogr Kinesiol 2013;23:362-8.
28. Kaya Aytutuldu G, Birinci T, Tarakcı E. Musculoskeletal pain and its relation to individual and work-related factors: a cross-sectional study among Turkish office workers who work using computers. Int J Occup Saf Ergon 2020;28:790-7.

Original Article

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An Altmetric Analysis of Top 100 Cited Articles on Perinatal Infection

Perinatal Enfeksiyon Konusunda En Çok Alıntı Yapılan 100 Makalenin Altmetrik Analizi

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ABSTRACT

Objective: Pregnant women and their fetuses are at increased risk of complications of viral, bacterial, and parasitic infections. For most infections, effective preventive strategies are available. Scientific studies on perinatal infections show advances in this field. The primary objective of this study was to evaluate the social attention paid to highly cited articles on perinatal infection in the last decade. Factors of altmetrics performance, including twitter mentions and the correlation between altmetrics and traditional citation counts were analyzed.

Methods: We created the 100 top-cited articles (T100) list from the Web of Science database and altmetric.com website among 4,240 perinatal infection articles.

Results: The most cited article "Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia" by Zhu H. published in the Translational Pediatrics Journal. The T100 list included 75 original scientific research publications and 25 review articles. On Twitter, 80 of the T100 articles were shared. Of the ten most tweeted articles, five were about 2019-nCoV, four were about Hepatitis B virus, and one was about Zikavirus. The number of AAS, average citations, and the number of tweets (NT) increased statistically significantly as the years increased. A statistically significant and strong correlation was found between AAS and the number of tweets.

Conclusion: This study reflects the most influential publications to identify the trends of current studies and provides some directions

ÖZ

Amaç: Hamile kadınlar ve fetüsleri viral, bakteriyel ve paraziter enfeksiyonların komplikasyonları açısından yüksek risk altındadır. Çoğu enfeksiyon için etkin önleyici stratejiler mevcuttur. Perinatal enfeksiyonlarla ilgili bilimsel çalışmalar bu alandaki gelişmeleri göstermektedir. Bu çalışmanın esas amacı, son on yılda perinatal enfeksiyon konusunda en çok alıntı yapılan makalelere gösterilen toplumsal ilgiyi değerlendirmektir. Altmetrik performans faktörleri, Twitter'de bahsedilenler ve altmetrikler ile geleneksel atıf sayıları arasındaki korelasyon da dahil olmak üzere analiz edildi.

Yöntemler: Dört bin iki yüz kırk perinatal enfeksiyon makalesi arasından Web of Science veri tabanından ve altmetric.com web sitesinden en çok atıf alan 100 makalenin listesini (T100) oluşturduk.

Bulgular: En çok alıntı yapılan makale olan ve Zhu H. tarafından yazılan "2019-nCoV pnömonisi olan annelerden doğan 10 yenidoğanın klinik analizi" Translational Pediatrics Journal'da yayınlandı. T100 listesinde 75 orijinal bilimsel araştırma yayını ve 25 inceleme makalesi yer aldı. Twitter'de T100 yazılarından 80'i paylaşıldı. En çok tweetlenen on makaleden beşi 2019-nCoV, dördü Hepatit B virüsü ve biri ZİKA virüs hakkındaydı. AAS sayısı, ortalama atıf sayısı ve tweet sayısı yıllar arttıkça istatistiksel olarak önemli ölçüde arttı. AAS ile tweet sayısı arasında istatistiksel olarak anlamlı ve güçlü bir ilişki bulundu.

Sonuç: Bu çalışma, mevcut çalışmaların eğilimlerini belirlemek için en etkili yayınları yansıtmakta ve araştırmacılara yardımcı olmak

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for future studies to help researchers. Also, it presents a view on the subject of the level of interest shown by the scientific world on social media platforms to the most cited articles on the subject of perinatal infection.

Keywords: Perinatal infection, altmetric, social media, top-cited article, twitter

için gelecekteki çalışmalar için bazı yönergeler sunmaktadır. Ayrıca perinatal enfeksiyon konusunda en çok atıf alan makalelere bilim dünyasının sosyal medya platformlarında gösterdiği ilgi düzeyi konusunda bir görüş sunmaktadır.

Anahtar Sözcükler: Perinatal enfeksiyon, altmetrik, sosyal medya, en çok atıf alan makale, twitter

Introduction

Infections during pregnancy are more common and complicated due to immigration, international travel, increasing viral morbidity, reduced primary and annual influenza vaccination (1,2). It is possible to prevent perinatal infections by implementing adequate strategies, more sensitive diagnostic techniques, and postnatal retrospective screening programs on time (3).

Citations are the basis for metrics like the h-index and its derivatives, which are used to evaluate the productivity and impact of individual researchers or the impact factor (IF) which is used to evaluate the scientific impact of journals (4-6). Traditionally, assessing the quality of publications based on the number of citations does not precisely reflect the quality (7,8). Bibliometric analysis is a statistical evaluation of scientific publications and provides an effective method to measure and compare the scientific value and impact of articles using a quantitative appraisal of citations, articles, and journals (9,10). A new score called Altmetric Attention Score (AAS) was created to measure the impact of scientific articles on social media (11). The AAS is qualitative data that is complementary to traditional citation-based metrics (12). However, in comparison to traditional citation metrics, altmetrics measure the impact of an article after publication, based on its number of mentions across various online sources. The article's final AAS reflects the summation of these weighted mentions (13). The AAS and the altmetric donut were developed to measure how much and what kind of attention a study received. The color of the source that gives the highest score to the research takes up more place in the donut. Each color on the altmetric donut symbolizes a different source of attention and the altmetric score is written in the donut's center (Figure 1). Social media attention following the publication of an article has previously been shown to correlate with the subsequent citation rate (14,15). Medical journals use social media, including blogs and commercial platforms such as Facebook and Twitter, to share medical information (16,17).

The objective of this study is to provide bibliometric and altmetric overviews and visualizations of the perinatal infection research, as well as to evaluate the association between traditional bibliometric analysis and altmetric analysis. In addition, we aimed to analyze the impact of Twitter on both metrics in terms of scientific knowledge dissemination.

Methods

Study Design

Our research was a retrospective clinical investigation with a level of evidence of three or group B based on the Scottish Intercollegiate Guidelines Network (SIGN) (18). The "perinatal infection" keyword was used in the Web of Science (WoS) Core Collection database (Philadelphia, Pennsylvania, United States) to find the articles (date of access: April 12, 2021) between 2011 and 2021. No language restrictions were set. The data was entered and analyzed using Microsoft Excel files. The IF's of journals were recorded based on the 2019 Clarivate Journal Citation Reports. The quartile (Q) scores and H-index of journals were determined using the 2020 Scimago Journal and Country Rank (19). Study types and levels of evidence were determined using SIGN 100. The bibliometric data of the T100 list (Table 1) was visualized using the VOSviewer software version 1.6.16 (20). The findings of country coupling and keyword co-occurrence analyses were visualized on maps. Altmetric attention scores were obtained by downloading the "Altmetric it" function from the Altmetric.com website (21-24). The website created AAS automatically using a mechanism based on a weighted average of each article's attention. Additionally, we determined how many times each article was shared on Twitter.

Each author certified that the study was conducted following the ethical principles of the Helsinki Declaration. This study did not require ethical approval as it performed bibliometric and altmetric analysis of currently published articles on perinatal infections.

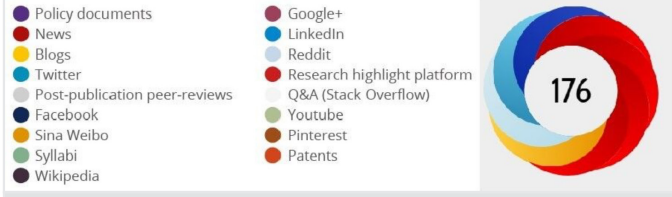

Figure 1. Altmetric donuts the altmetric donut were developed to measure how much and what kind of attention a study receives. The color of the source that gives the highest score to the research takes up more place in the donut. Each color on the altmetric donut symbolizes a different source of attention and the altmetric score is written in the donut's center

Table 1. Top 100 article by metrics (T100 list)

Rank	Title	Publication year	First author	TCN	ACpY	AAS	NT's
1	Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia	2020	Zhu, Huaping	477	238,5	442	249
2	Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014	2014	Besnard, M.	412	51,5	70	2
3	Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load	2016	Pan, Calvin Q.	258	43	161	104
4	A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection	2011	Han, Guo-Rong	245	22,27	9	0
5	The global burden of listeriosis: a systematic review and meta-analysis	2014	de Noordhout, Charline Maertens	233	29,13	60	13
6	Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices	2018	Schillie, Sarah	212	53	197	178
7	Congenital Zika Virus Infection Beyond Neonatal Microcephaly	2016	de Oliveira Melo	196	32,67	233	85
8	Vertical Transmission of Hepatitis C Virus: Systematic Review and Meta-analysis	2014	Benova, Lenka	170	21,25	33	19
9	Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies	2020	Zaigham,Mehreen	169	84,5	676	762
10	Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis	2016	Brown, Robert S	162	27	19	6
11	Understanding the mental health of youth living with perinatal HIV infection: lessons learned and current challenges	2013	Mellins, Claude A	156	17,33	5	2
12	Mother-to-infant transmission of hepatitis B virus infection: Significance of maternal viral load and strategies for intervention	2013	Wen, Wan-Hsin	152	16,89	2	2
13	Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection	2011	Siegfried, Nandi	146	13,27	7	2
14	HIV-Specific Antibodies Capable of ADCC Are Common in Breastmilk and Are Associated with Reduced Risk of Transmission in Women with High Viral Loads	2012	Mabuka, Jennifer	145	14,5	34	5
15	An Algorithm for Risk Assessment and Intervention of Mother to Child Transmission of Hepatitis B Virus	2012	Pan, Calvin Q.	140	14	0	0
16	Estimating the Probability of Neonatal Early-Onset Infection on the Basis of Maternal Risk Factors	2011	Puopolo, Karen M	140	12,73	3	2
17	Effects of Maternal Screening and Universal Immunization to Prevent Mother-to-Infant Transmission of HBV	2012	Chen, Huey-Ling	139	13,9	5	1
18	Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus	2015	Chen, Huey-Ling	136	19,43	15	19
19	Neonatal sepsis: Progress towards improved outcomes	2014	Shane, Andi L.	136	17	4	
20	Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: Experience in the United States and implications for a potential group B streptococcal vaccine	2013	Schrag, Stephanie J	136	15,11	34	9
21	Listeriosis in human pregnancy: a systematic review	2011	Lamont, Ronald F	134	12,18	11	0

Table 1. Continued

Rank	Title	Publication year	First author	TCN	ACpY	AAS	NT's
23	Tenofovir versus Placebo to Prevent Perinatal Transmission of Hepatitis B	2018	Jourdain, G	125	31,25	177	197
24	Three Postpartum Antiretroviral Regimens to Prevent Intrapartum HIV Infection	2012	Nielsen-Saines, Karin	120	12	59	56
25	Strategies to control hepatitis B: Public policy, epidemiology, vaccine and drugs	2015	Locarnini,Stephen	117	16,71	4	6
26	Early antiretroviral therapy improves neurodevelopmental outcomes in infants	2012	Laughton, Barbara	114	11,4	6	1
27	No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception	2015	Mandelbrot,Laurent	111	15,86	13	4
28	Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus	2014	Greenup,Astrid-Jane	107	13,38	17	3
29	Telbivudine Prevents Vertical Transmission From HBeAg-Positive Women With Chronic Hepatitis B	2012	Pan, Calvin Q	107	10,7	9	0
30	Neonatal Infection and 5-year Neurodevelopmental Outcome of Very Preterm Infants	2013	Mitha, Ayoub	103	11,44	3	3
31	TORCH Infections	2015	Neu, Natalie	102	14,57	7	1
32	Prevention of Chronic Hepatitis B after 3 Decades of Escalating Vaccination Policy, China	2017	Cui, Fuqiang	99	19,8	9	8
33	Trichomonas vaginalis as a Cause of Perinatal Morbidity: A Systematic Review and Meta-Analysis	2014	Silver, Bronwyn J	99	12,38	22	2
34	Neurocognitive Outcome of Children Exposed to Perinatal Mother-to-Child Chikungunya Virus Infection: The CHIMERE Cohort Study on Reunion Island	2014	Gerardin, Patrick	98	12,25	75	12
35	Telbivudine or Lamivudine Use in Late Pregnancy Safely Reduces Perinatal Transmission of Hepatitis B Virus in Real-Life Practice	2014	Zhang, Hua	95	11,88	15	4
36	Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease	2016	Nelson, Noele P	92	15,33	5	11
37	Impact of HIV Severity on Cognitive and Adaptive Functioning During Childhood and Adolescence	2012	Smith, Renee	92	9,2	1	2
38	Policy Statement-Recommendations for the Prevention of Perinatal Group B Streptococcal (GBS) Disease	2011	Baker, Carol J	92	8,36	13	
39	Tenofovir Disoproxil Fumarate for Prevention of Vertical Transmission of Hepatitis B Virus Infection by Highly Viremic Pregnant Women: A Case Series	2012	Pan, Calvin Q	89	8,9	3	0
40	A national review of vertical HIV transmission	2012	Forbes, John C	85	8,5	6	4
41	Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes	2011	Connell, Laura E	75	6,82	0	0
42	Antiretroviral Drugs in the Cupboard are Not Enough: The Impact of Health Systems' Performance on Mother-to-Child Transmission of HIV	2011	Barker, Pierre M	75	6,82	3	0
43	Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets	2017	Spearman, C.Wendy	74	14,8	13	20
44	Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review	2020	Juan, J.	73	36,5	37	
45	Factors associated with vaccine failure and vertical transmission of hepatitis B among a cohort of Canadian mothers and infants	2011	Singh, A. E	71	6,45	8	1

Table 1. Continued

Rank	Title	Publication year	First author	TCN	ACpY	AAS	NT's
47	Hepatitis C in pregnancy: screening, treatment, and management	2017	Hughes, Brenna L.	68	13,6	30	41
48	Hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission	2016	Dionne-Odom, Jodie	67	11,17	24	32
49	The challenges of success: adolescents with perinatal HIV infection	2013	Mofenson, Lynne M	67	7,44	1	2
50	A Framework for Elimination of Perinatal Transmission of HIV in the United States	2012	Nesheim, Steven	67	6,7	6	0
51	Perinatal outcomes associated with maternal HIV infection: a systematic review and meta-analysis	2016	Wedi, Chrystelle O.	66	11	33	24
52	The risk of perinatal hepatitis B virus transmission: hepatitis B e antigen (HBeAg) prevalence estimates for all world regions	2012	Ott, Joerdis J.	66	6,6	17	10
53	COVID-19 in Children, Pregnancy and Neonates: A Review of Epidemiologic and Clinical Features	2020	Zimmermann, Petra	65	32,5	969	23
54	Human Cytomegalovirus Infant Infection Adversely Affects Growth and Development in Maternally HIV-Exposed and Unexposed Infants in Zambia	2012	Gompels, U. A.	65	6,5	3	2
55	Impact of Middle East Respiratory Syndrome coronavirus (MERS-CoV) on pregnancy and perinatal outcome	2016	Alserehi, Haleema	64	10,67	60	65
56	Prevention of Vertical Transmission of Hepatitis B An Observational Study	2014	Kubo, Ai	64	8	61	20
57	An Epidemiologic Update on Hepatitis C Infection in Persons Living With or at Risk of HIV Infection	2013	Kim, Arthur Y	64	7,11	0	0
58	Hepatitis C Virus in Pregnancy	2013	Prasad, Mona R.	64	7,11	0	0
59	A systematic scoping review of COVID-19 during pregnancy and childbirth	2020	Elshafeey, Farida	63	31,5	177	210
60	Cesarean Section Reduces Perinatal Transmission of Hepatitis B Virus Infection From Hepatitis B Surface Antigen-Positive Women to Their Infants	2013	Pan, Calvin Q	63	7	8	4
61	Outcomes of Infants Born to Women Infected With Hepatitis B	2015	Schillie, Sarah	62	8,86	30	28
62	Antiretroviral Treatment of US Children With Perinatally Acquired HIV Infection: Temporal Changes in Therapy Between 1991 and 2009 and Predictors of Immunologic and Virologic Outcomes	2011	Van Dyke, Russell B	62	5,64	0	0
63	Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis	2020	Allotey, John	61	30,5	1307	743
64	Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection	2013	Celen, Mustafa Kemal	61	6,78	60	0
65	Anti-viral therapy for prevention of perinatal HBV transmission: extending therapy beyond birth does not protect against post-partum flare	2014	Nguyen, V	59	7,38	3	5
66	Group B streptococcal epidemiology and vaccine needs in developed countries	2013	Melin, Pierrette	59	6,56	0	0
67	Longitudinal Study of Emerging Mental Health Concerns in Youth Perinatally Infected With HIV and Peer Comparisons	2012	Gadow, Kenneth D	59	5,9	2	3
68	Middle East Respiratory Syndrome Coronavirus Infection During Pregnancy: A Report of 5 Cases From Saudi Arabia	2016	Assiri, Abdullah	58	9,67	20	15

Table 1. Continued

Rank	Title	Publication year	First author	TCN	ACpY	AAS	NT's
70	Correlates of Mother-to-Child Transmission of HIV in the United States and Puerto Rico	2012	Whitmore, Suzanne K	58	5,8	4	1
71	Hepatitis C virus infection during pregnancy and the newborn period - are they opportunities for treatment?	2011	Arshad, M	58	5,27	6	0
72	Prognostic markers of symptomatic congenital human cytomegalovirus infection in fetal blood	2011	Fabbri, E	57	5,18	0	0
73	Chronic hepatitis B in Asia-new insights from the past decade	2011	Chan, Henry Lik-Yuen	57	5,18	3	0
74	Hepatitis C Virus Infection Among Women Giving Birth - Tennessee and United States, 2009-2014	2017	Patrick, Stephen W	56	11,2	272	78
75	Integrated prevention of mother-to-child transmission for human immunodeficiency virus, syphilis and hepatitis B virus in China	2015	Wang, Ai-Ling	56	8	4	0
76	Influence of Age at Virologic Control on Peripheral Blood Human Immunodeficiency Virus Reservoir Size and Serostatus in Perinatally Infected Adolescents	2014	Persaud, Deborah	56	7	6	10
77	Cytomegalovirus-specific T-cell reactivity in biliary atresia at the time of diagnosis is associated with deficits in regulatory T cells	2012	Brindley, Stephen M	56	5,6	1	1
78	Performance of HIV-1 DNA or HIV-1 RNA Tests for Early Diagnosis of Perinatal HIV-1 Infection during Anti-Retroviral Prophylaxis	2012	Burgard, Marianne	56	5,6	5	0
79	An Analysis of 38 Pregnant Women With COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2	2020	Schwartz, David A.	55	27,5	457	341
80	Chronic hepatitis B infection in adolescents who received primary infantile vaccination	2013	Wu, Tzu-Wei	55	6,11	90	88
81	Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: Findings from the Antiretroviral Pregnancy Registry	2012	Brown, Robert S	54	5,4	7	6
82	Clues to the Etiology of Bile Duct Injury in Biliary Atresia	2012	Mack, Cara L.	54	5,4	1	1
83	Cytomegalovirus-associated biliary atresia: An aetiological and prognostic subgroup	2015	Zani, Augusto	53	7,57	2	3
84	Maternal-fetal transmission and adverse perinatal outcomes in pregnant women infected with Zika virus: prospective cohort study in French Guiana	2018	Pomar, Leo	52	13	69	98
85	HIV-Associated Cognitive Impairment in Perinatally Infected Children: A Meta-analysis	2016	Phillips, Nicole	52	8,67	17	
86	The National Perinatal Hepatitis B Prevention Program, 1994-2008	2012	Smith, Emily A.	52	5,2	21	7
87	Testing for Zika virus infection in pregnancy: key concepts to deal with an emerging epidemic	2017	Eppes, Catherine	51	10,2	34	40
88	Estimated Number of Infants Born to HIV-Infected Women in the United States and Five Dependent Areas, 2006	2011	Whitmore, Suzanne K.	51	4,64	0	0
89	Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C Virus-Infected Women	2016	Kuncio, Danica E	49	8,17	27	8
90	The effects of telbivudine in late pregnancy to prevent intrauterine transmission of the hepatitis B virus: a systematic review and meta-analysis	2012	Deng, Min;	49	4,9	1	3
91	Hepatitis B and C in pregnancy: a review and recommendations for care	2014	Dunkelberg, J. C.	48	6	20	14

Table 1. Continued

Rank	Title	Publication year	First author	TCN	ACpY	AAS	NT's
93	Human Immunodeficiency Virus Disease Severity, Psychiatric Symptoms, and Functional Outcomes in Perinatally Infected Youth	2012	Nachman, Sharon	48	4,8	7	7
94	Mother-to-Infant Transmission of Hepatitis B Virus: A Chinese Experience	2011	Shao, Zhong-Jun	47	4,27	0	0
95	Antiviral Therapy for Chronic Hepatitis B in Pregnancy	2013	Pan, Calvin Q	46	5,11	9	13
96	Optimal Time on HAART for Prevention of Mother-to-Child Transmission of HIV	2011	Chibwesha, Carla J	46	4,18	6	5
97	Congenital and perinatal complications of chikungunya fever: a Latin American experience	2016	Torres, Jaime R.	45	7,5	28	30
98	Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers	2014	Yi, Wei	45	5,63	0	
99	Perinatal Infections and Neurodevelopmental Outcome in Very Preterm and Very Low-Birth-Weight Infants A Meta-Analysis	2013	van Vliet, Elvira O	44	4,89	18	20
100	Perinatal aspects on the covid-19 pandemic: a practical resource for perinatal-neonatal specialists	2020	Mimouni, Francis	43	21,5	69	87

TCN: Total citation number, ACpY: Average citation per year, AAS: Altmetric attention score, NTs: Number of tweet

Table 2. Study types and level of evidence by SIGN

Type-subtype	Number of articles	Level of Evidence	AAS M (Q1- Q3)	TCN M(Q1-Q3)	ACN M (Q1-Q3)	NT M(Q1-Q3)
Meta-analysis, systematic review	16	1	30.5 (17-60)	117 (66-162)	15.7 (11.4-30.5)	16 (2- 56)
Randomized controlled trial	5	1				
Randomized clinical trial	1	1				
Prospective cohort study	12	2	7 (3-21.5)	60.5 (51.5-96.5)	7.44 (5.5-11.66)	4.5 (0-15.5)
Ambispective cohort study	1	2				
Non-randomized clinical trial	1	2				
Retrospective cohort study	9	3	6 (2-27)	61 (55-107)	6.82 (5.8 -12.73)	3 (1-8)
Case-control study	9	3				
Case reports	3	3				
Case Series	3	3				
Cross-sectional study	4	3				
Comparative study	4	3				
Review	24	4	9 (4-34)	67 (57-102)	11.17 (7.11-16.71)	6 (0-32)
Practice guideline	6	4				
Editorial	1	4				
Historical article	1	4				
p-value			0.024	0.090	0.001	0.079

TCN: Total citation number, ACN: Average citation number, AAS: Altmetric attention score, NT: number of tweets, M [Q1 Q3]. M: Median, Q1: Quartile 1 (p25), Q3: Quartile 3 (p75), P-value was obtained from Kruskal-Wallis or Mann-Whitney U test Scottish Intercollegiate Guidelines Network (SIGN)*

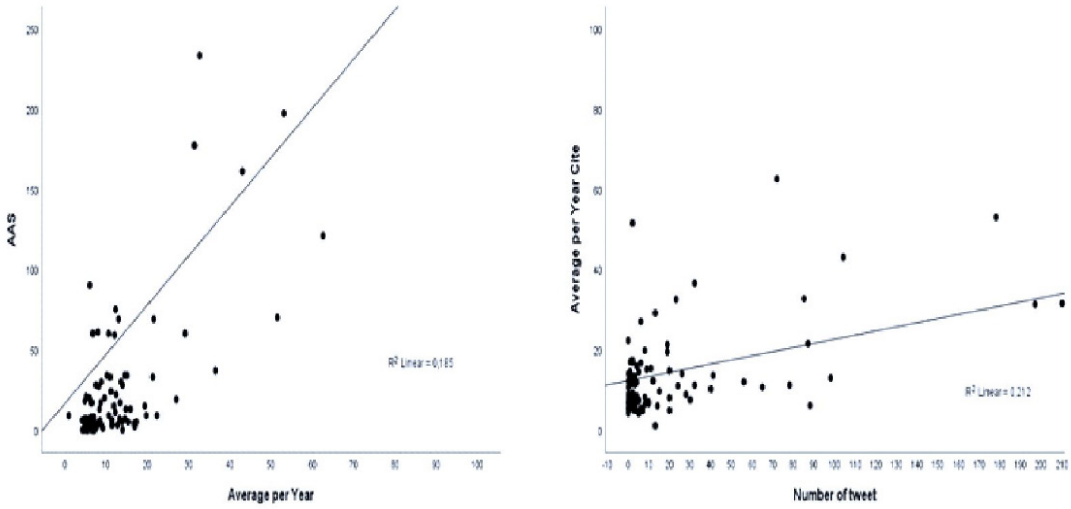

Figure 2. Scatter plot of the relationship between altmetric score average citations per year and number of tweets. There was a strong positive correlation between AAS and the average per year. There was a strong positive correlation between the average of per year and Tweet

Table 3. Top-100 cited articles according to subject categories

Subject categories	Number of articles	AAS median (IQR)	Total cita. median (IQR)	Avarage cita. median (IQR)	Tweet median (IQR)
Transmission risk factors	23	7 (3-30)	111 (62-140)	12,73 (6.78 -15,.86)	2 (1-19)
Epidemiology	19	27 (3-60)	59 (52-68)	10.2 (6.6-15,33)	11 (0-40)
Prevention	18	13 (4-21)	93.5 (64-117)	11.53 (8-16.71)	5.5 (2-9)
Clinical features	16	64.5 (15.5-205)	66.5 (59.5-151.5)	26 (10.17-44)	48.5 (10-148.5)
Perinatal outcomes	12	5.5 (2.5-19)	83.5 (55.5-101)	93 (6.25-11.84)	2 (2-7.5)
Diagnostic methods	3	1 (0-5)	56 (56-57)	5.6 (5.18-5.6)	0 (0-1)
Others	9	2 (1-7)	54(53-56)	6,11 (5.4-7)	4 (2-8)
P value		0.001	0.004	0.001	0.014

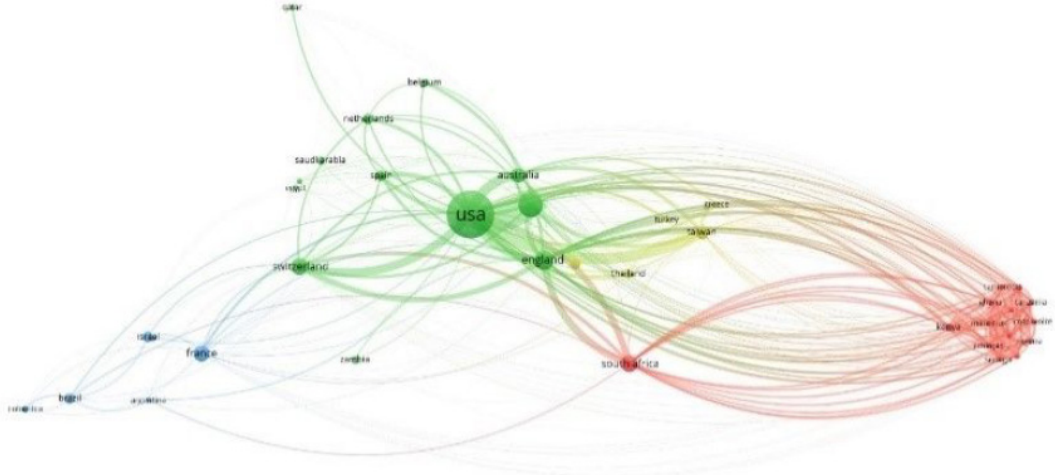

Figure 3. Distribution and intersection points of top 100 cited articles. Countries analyses were performed. For each of the 41 countries on the T100 list, the total strength of bibliographic coupling linkages with other countries was measured and visualized

Statistical Analysis

All analyses were performed by IBM SPSS for windows version 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were described using the median and interquartile range (IQRs), whereas categorical variables were defined using percentages. The comparative analysis of the parameter values according to the publication years and main subject were made with the Kruskal-Wallis test and the post hoc tests were made with the Dunn test. Mann-Whitney U test was used for comparisons based on Q categories. The Shapiro-Wilk test was used to determine the parameters' conformity to the normal distribution. Sperman or Pearson correlation coefficients were calculated to detect the linear relationship between numerical variables. Beta coefficients were estimated by univariate linear regression analysis. $P<0.05$ was considered statistically significant.

Results

Using the term "infection" in the WoS search, we found 852,880 publications between 2011 and 2021. Later, the term "perinatal" was added and the total number of publications decreased to 4240. All of the articles on the T100 list were published in English.

Total Citation Number (TCN) and AAS Analysis

The median values for TCN and AAS scores were 4.5 (IQR 43-477) and 172 (IQR 0-1307), respectively in the T100 list. The citation number was ranked between 477 and 43. The T100 list was ranked between AAS 1,377 and 0. There were ten articles on the T100 list that did not have AAS yet. The most cited article was published by Zhu et al. (25) in April 2020 and received

Table 4. Distrubition of microorganisms

Microorganism	n	%
HBV	35	35.7
HIV	24	24.5
nCoV	9	9.2
HCV	7	7.1
CMV	5	5.1
ZIKA virus	5	5.1
GBS	4	4.1
Chikungunya virus	2	2.0
Listeria	2	2.0
MERS-CoV	2	2.0
TORCH	1	1.0
Trichomonas vaginalis	1	1.0
Bacterial infection	1	1.0

HBV: Hepatit B virus, HIV: Human immunodeficiency virus, nCoV: Nex Covid, HCV: Hepatit C virus, CMV: Cytomegalovirus, GBS: Guillain-Barré syndrome, MERS-CoV: Middle East respiratory syndrome-covid, TORCH: Toxoplasma gondii

Table 5. Correlation analysis

		Total citations	Number of tweets	Average per Year	Number of years since publication	H index	Journal impact factor	Q kategory	
AAS	r	0.157	0.808**	0.430**	-0.575**	0.064	0.136	0.074
	p	0.118	0.001	0.001	0.001	0.524	0.184	0.462
Total citations	r	1	0.167	0.748**	-0.152	0.085	0.209*	0.223*
	p		0.097	0.001	0.132	0.398	0.040	0.026
Number of tweets	r		1	0.461**	-0.572**	0.098	0.184	0.102
	p			0.001	0.001	0.331	0.071	0.312
Average per year	r			1	-0.505**	-0.067	0.055	0,378**
	p				0.001	0.507	0.594	0.001
Number of years since the publication	r				1	0.001	-0.132	-0.060
	p					1.000	0.197	0.552
H index	r					1	0.840**	-0.186
	p						0.001	0.065
Journal impact factor	r						1	-0.135
	p							0.187

a TCN of 477 and AAS of 442 at the Translational Pediatrics journal. The article by Allotey et al. (26) had the highest value with 1307 AAS on the T100 list and it was published in British Medical Journal. The four of the articles with the highest AAS were among the top 10 articles with the highest CN.

Twitter Analysis

On Twitter, 80 articles from the T100 list were found to be shared. Of the ten most tweeted articles, five were about 2019-nCoV, four were about Hepatitis B virus (HBV), and one was about Zikavirus. The most-tweeted article was "Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies" with 762 retweets (27).

Journal Perspective

The T100 articles were published in 59 journals with the number of articles per journal ranging from 1 to 8. Pediatrics, Clinical Infectious Diseases, and Journal of Hepatology were the three leading journals in which the majority of the articles were published. The most cited journal was Translational Pediatrics with 477 citations, followed by Eurosurveillance with 412 citations and New England Journal of Medicine with 258 citations. The most tweeted articles were published in Acta Obstetrıcıa et Gynecologıca Scandinavica, British Medical Journal and Archives of Pathology & Laboratory Medicine, respectively. According to SJCR, all journals received Q1 scores, except for five journals that received Q2 scores.

Article Types

The 75 articles on the T100 list were original scientific researches and 25 articles were review articles (Table 2). Also, there were 16 meta-analyses and 5 randomized controlled trials. The AAS values of studies with evidence level 1 were found to be statistically significantly higher than those with level 3 (p=0.024). Studies with evidence level 1 had statistically substantially higher average and total citation values than studies with evidence levels 2 and 3 (p<0.05).

Research Topics

When we evaluated the T100 list in terms of the main topic, the majority of articles were related to risk factors for transmission (n=23), epidemiology (n=19), prevention (n=18), clinical features, and outcomes (n=16) of perinatal infections (Table 3). The most frequent microorganisms were HBV, followed by human immunodeficiency virus (HIV) and 2019-nCoV (Table 4).

Distribution of Countries

The 100 top-cited perinatal infections articles were from 41 countries. The United States had the highest total number of publications (59), followed by China (16), England (10), Switzerland and South Africa (8), France (7) and Australia (6). The country with the most citations was the USA with 5193 citations, followed by China with 1997 citations and France with 957 citations.

Correlation Analysis

The number of AAS, average citations, and the number of tweets increased statistically significantly as the years increased (p<0.001). The AAS numbers, total citation number, the average citation, and tweet counts of studies with main subjects "clinical features" and "outcomes" were found to be statistically significantly higher than studies on other subjects (p<0.05). A statistically significant and strong correlation was found between AAS and the number of tweets (r=0.808, p=0.001). As the number of tweets got higher, the AAS was likely to increase as a consequence. There was a positive correlation between AAS and the average per year, and a negative statistically significant

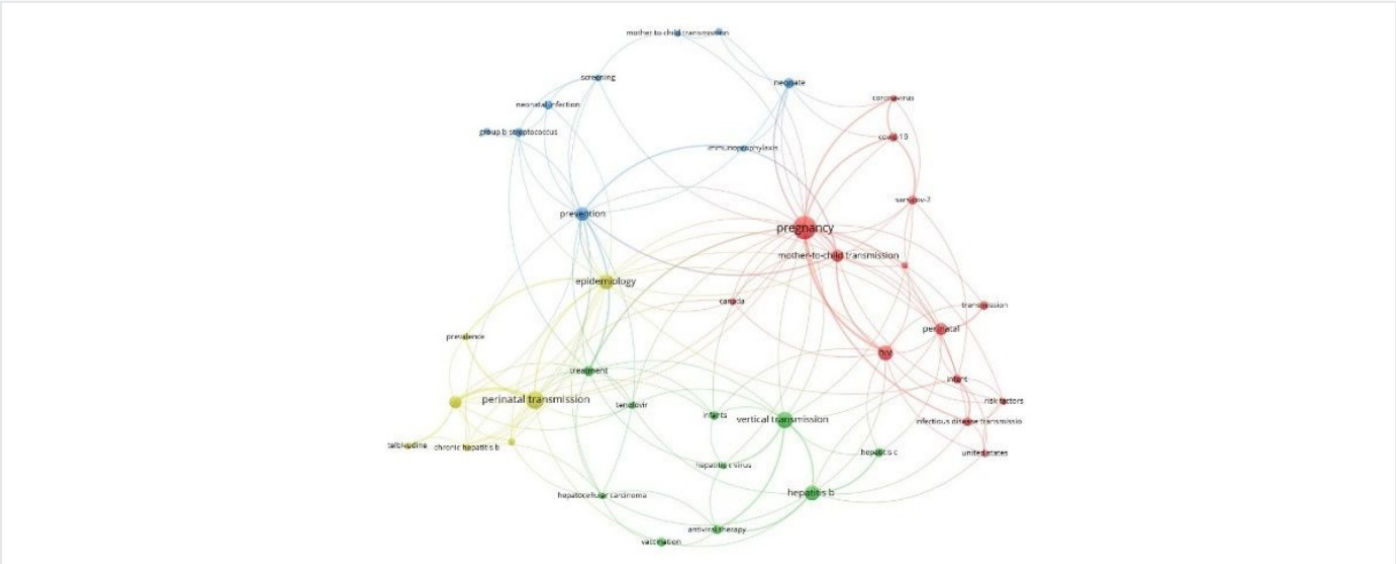

Figure 4. Distribution and intersection points of top 100 cited articles Co-occurrence analysis of high-frequency keywords was performed. The minimal number of keyword co-occurrences criteria was chosen to be 2. The criteria were met by 25 of the 43 retrieved keywords related to perinatal infection. The network was used to cluster related keywords, and the five major clusters were represented by the colors, red, green, blue, yellow, and purple, respectively

moderate correlation between AAS and the variable of the number of years since publication ($p<0.05$). A statistically significant weak correlation was found between the journal IF and total citation numbers ($r=0.209$, $p=0.040$). A statistically significant and strong correlation was found between the journal IF and the h index ($r=0.840$, $p=0.001$). Positive and statistically significant weak correlations were found between the Q category, total citation number and average per year ($p<0.05$).

The correlation between AAS, TCN, NYsP, and journal IF, H-index, and Q categories are shown in Table 5. There was a strong positive correlation between AAS and the average per year ($r=0.430$; $p=0.001$) and there was a strong positive correlation between the average of per year and the number of tweets ($r=0.461$; $p=0.001$) (Figure 2).

Visualization Analysis

For each of the 41 countries on the T100 list, the total strength of bibliographic coupling linkages with other countries was measured and visualized (Figure 3). Large nodes refer to countries that are productive and efficient. The degree of communication and collaboration across nations is shown by the thickness and distance of linkages between nodes (28). United States Department of Health Human Services (28), National Institutes of Health Nih USA (25), and Nih National Institute of Allergy Infectious Diseases Niaid (13) were the leading institutions. Co-occurrence analysis of high-frequency keywords was performed. The minimal number of keyword co-occurrences criteria was chosen to be 2. The criteria were met by 25 of the 43 retrieved keywords related to perinatal infection. The network was used to cluster related keywords, and the five major clusters were represented by the colors, red, green, blue, yellow, and purple, respectively (Figure 4). "Pregnancy" and "perinatal transmission" were the most frequently used keywords.

Discussion

In previous studies, AAS was detected at different ranges. Moon et al. (29) found the AAS between 7,301-34,789 in their study. Li et al. (30) stated AAS values between 57 and 1. We found the AAS values between 1,377 and 0. We found that there was no correlation between TCN and AAS as Celik et al. (31) did not find. The wide spectrum of AAS is because articles on the T100 list do not get the same level of attention in social media.

Our findings show that epidemiological studies investigating the prevalence, clinical features, and outcomes of perinatal infections have attracted great interest both in the academic community and in social media. The AAS increases in response to both positive and negative comments, this should also be considered in the assessment. Even if an article receives few citations, it might gain a lot of attention on social media. The article by Allotey et al. (26) had AAS of 1,307, but it was only 61 times cited. This can be attributed to the subject of the article attracting social media attention. Only the four of the articles with the highest AAS were among the top 10 articles with the highest TCN.

Altmetric attention scores and the number of tweets had a weak positive correlation with average citation per year (ACpY). This means that articles which have been cited regularly over the years and remain relevant are more valuable on social media and Twitter. Furthermore, despite analyzing only the last decade, we found a strong negative correlation between the "AAS" of the T100 articles and the number of years since publication. The rising number of social media users globally, as well as social media's growing interest in studies about the perinatal infections literature in the last few years, might explain these findings.

The "level of evidence" indicates how likely it is that a research paper's conclusions are correct. It is related to the study's design and how well it is carried out. The highest AAS and total citation number values were found in articles with the level of evidence 1 in our study, as expected. The h-index is a scientometric indicator at the researcher level that is based on a simple combination of publication and citation counts. In this article, we found a statistically significant and strong correlation between the journal IF and the h index. One thing to remember about the h-index is that it correlates with the length of a researcher's career and it can also be inflated by self-citation.

In our study, we determined a statistically significant weak correlation between the journal IF and total citation number. Also, we found that there was no correlation between IF and AAS or the number of tweets. The fact that AAS and number of tweets were positively correlated with ACpY might explain this situation. The IF would only measure the interests of other researchers in an article, not its value and usefulness. Previous studies have discovered that journals with social media accounts such as Twitter has significantly higher AAS than those without (32) and that tweets can predict highly cited articles within the first 3 days of article publication. When we investigated the relationship between AAS and average citation per year, we discovered that articles that drew attention in the academic community retained their relevance in social media.

Almost half of the included articles were from the USA and China which was consistent with previous studies (33,34). This may be closely related to the influence and scientific output of the field of perinatal infection in the USA and China. The developed countries such as the USA pay more attention to the topic and have more funding. If we consider China, it is the country where the COVID pandemic started and spread to the world.

Study Limitations

Current definitions of altmetrics are shaped and limited by active platforms, technical capabilities, and the Altmetric.com website. Given Altmetric does not include all media sources and the relationship between AAS and citations may change over time. First, the current study was only based on journal studies from the WoS database. Therefore, there might be some overlooked literature. When we analyzed the origin country, our study was based on the institution address of the corresponding author if the author changed the address, there might be statistical bias. Altmetrics do not cover the demographics of scientists and the nature of each mention (positive or negative) Furthermore, the

reliability of commenters and the veracity of their opinions are under doubt due to the ease with which internet data may be manipulated.

Conclusion

There is no study examining the 100 most cited articles on perinatal infections. This study reflects the most influential publications to identify the trends of current studies and provides some directions for future studies to help researchers. Also, it presents a view on the subject of the level of interest shown by the scientific world on social media platforms to the most cited articles on the subject of perinatal infections.

Ethics

Ethics Committee Approval: Each author certified that the study was conducted following the ethical principles of the Helsinki Declaration. This study did not require ethical approval as it performed bibliometric and altmetric analysis of currently published articles on perinatal infections.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: D.B., H.B., Design: D.B., H.B., Data Collection or Processing: D.B., H.B., Analysis or Interpretation: D.B., H.B., Literature Search: D.B., H.B., Writing: D.B., H.B.

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References

1. Wilson RD. Acute Perinatal Infection and the Evidenced-Based Risk of Intrauterine Diagnostic Testing: A Structured Review. Fetal Diagn Ther 2020;47:653-64.
2. Hwang JS, Friedlander S, Rehan VK, Zangwill KM. Diagnosis of congenital/perinatal infections by neonatologists: a national survey. J Perinatol 2019;39:690-6.
3. Palasanthiran P, M Starr, Jones, C, Giles M (Eds). Management of Perinatal Infections, Sidney: Australasian Society for Infectious Diseases 2014:4.
4. Bulut E, Celebi ARC, Dokur, Dayi O. Analysis of trending topics in glaucoma articles from an altmetric perspective. Int Ophthalmol 2021;41:2125-37.
5. Hirsch JE. An index to quantify an individual's scientific research output. Proc Natl Acad Sci U S A 2005;102:16569-72.
6. Garfield E. The history and meaning of the journal impact factor. JAMA 2006;295:90-3.
7. Patthi B, Prasad M, Gupta R, Singla A, Kumar JK, Dhama K, Altmetrics – a collated adjunct beyond citations for scholarly impact: a systematic review. J Clin Diagn Res 2017;11:1620.
8. Bellini C. Cited or read? Lancet 2012;379:314.
9. Aria M and Cuccurullo C. Bibliometrix: An R-tool for comprehensive science mapping analysis. J Informetrics 2017;11:959-75.
10. Garfield E. Citation analysis as a tool in journal evaluation. Science 1972;178:471-9.
11. Araujo AC, Vanin AA, Nascimento DP, Gonzalez GZ, Costa LOP. What are the variables associated with Altmetric scores? Syst Rev 2021;10:193.
12. Priem J, Taraborelli D, Groth P, Neylon C. Altmetrics: A manifesto, 26 October 2010. http://altmetrics.org/manifesto.
13. Nocera AP, Boyd CJ, Boudreau H, Hakim O, Rais-Bahrami S. Examining the Correlation Between Altmetric Score and Citations in the Urology Literature. Urology 2019;134:45-50.
14. Eysenbach G. Can tweets predict citations? Metrics of social impact based on Twitter and correlation with traditional metrics of scientific impact. J Med Internet Res 2011;13:e123.
15. Thelwall M, Haustein S, Larivière V, Sugimoto CR. Do altmetrics work? Twitter and ten other social web services. PloS One 2013;8:e64841.
16. Fox CS, Bonaca MA, Ryan JJ, Massaro JM, Barry K, Loscalzo J. A randomized trial of social media from Circulation. Circulation 2015;131:28-33.s
17. https://s22.q4cdn.com/826641620/files/doc_financials/2021/q1/Q1'21_InvestorFactSheet.
18. Network SIGN (2019) Scottish Intercollegiate Guidelines Network; SIGN 100 (in A Guideline developer's handbook Re, November 2011) Healthcare Improvement Scotland 2019. https://www.sign.ac.uk/media/1052/sign100.
19. SCImago ndS. Scimago Journal & Country Rank 2020. https://www.scimagojr.com
20. Van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 2010;84:523-38.
21. Discover the attention surrounding your research 2020. https://www.altmetric.com.
22. Altmetric 2020. https://www.altmetric.com/products/free tools/bookmarklet.
23. The donut and Altmetric Attention Score—Altmetric 2020. https://www.altmetric.com /about-our-data/ the-donut-and-score.
24. AAS Calculation on altmetric website.https://help.altmetric.com / support/solutions/articles/6000060969-how-is-the-altmetric-attention-score calculated
25. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020;9:51-60.
26. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020;370:m3320.
27. Zaigham M,1 Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Et Gynecol Scandın 2020;99:823-9.

28. Zou X, Yue WL, Vu HL. Visualization and analysis of mapping knowledge domain of road safety studies. Accid Anal Prev 2018;118:131-45.
29. Moon JY, Yoon DY, Hong JH, Lim KJ, Baek S, Seo YL, et al. The Most Widely Disseminated COVID-19-Related Scientific Publications in Online Media: A Bibliometric Analysis of the Top 100 Articles with the Highest Altmetric Attention Scores. Healthcare (Basel) 2021;9:239.
30. Li C, Ojeda-Thies C, Renz N, Margaryan D, Perka C, Trampuz A. The global state of clinical research and trends in periprosthetic joint infection: A bibliometric analysis. Int J Infect Dis 2020;96:696-709.
31. Celik E, Dokur M, Borku Uysal B, Sengul Samancı N, Demırelli FH. Comparison of attention for cancer research on social media versus academia: An altmetric score analysis. International Journal of Hematology and Oncology 2020;30:32-42.
32. Wang X, Cui Y, Liu Q, Guo X. Social Media Attention Increases Article Visits: An Investigation on Article-Level Referral Data of PeerJ. Front Res Metr Anal 2017;2:11.
33. Chen LM, Liu YQ, Shen JN, Peng YL, Xiong TY, Tong X, et al. The 100 top-cited tuberculosis research studies. Int J Tuberc Lung Dis 2015;19:717-22.
34. Zhang Y, Huang J, Du L. The top-cited systematic reviews/meta-analyses in tuberculosis research: A PRISMA-compliant systematic literature review and bibliometric analysis. Medicine (Baltimore) 2017;96:e48.

Original Article

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Describing Effectiveness of Performing International Classification of Function, Disability and Health on Children with Cerebral Palsy

Uluslararası Fonksiyonellik, Özür ve Sağlık Sınıflandırması Kodlama Sisteminin Serebral Palsili Çocuklarda Uygulanarak Etkinliğinin Belirlenmesi

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ABSTRACT

Objective: Aim of this study was to investigate the effectiveness of performing the International classification of functioning, disability and health: children and youth version (ICF-CY) on the description of functioning, disability and health in children with cerebral palsy (CP).

Methods: Thirty children with diplegic or hemiplegic CP (13 girls: 17 boys) with a mean age of 9.13±2.2 years (6-13 years) participated in the study. For ICF core set, 35 categories were selected which were most suitable for children with CP. In addition, gait and balance tests, gross motor function measurement, Wee-FIM for Children Scale and Child Health Questionnaire-Mother/Father Report (CHQ-PF50) were also used. Body structure and function, activity and participation of each child and limiting and facilitating factors of their environment were coded.

Results: The ICF core set body functions, activity-participation, walking and balance tests, Gross Motor Function Measure-88 (GMFM-88), Pediatric Functional Independence Measure (WEEFIM) were found to be moderately correlated ($p<0.05$). There was a weak to moderate correlation between ICF core set body functions and activity-participation and CHQ-PF50 ($p<0.05$). There was a weak correlation between ICF core set environmental factors and walking and balance tests, GMFM-88, WEEFIM, and CHQ-PF50 ($p<0.05$).

Conclusion: We think that the ICF is an effective conceptual framework for defining functioning, disability and health in children with CP, that ICF system can be used as a reference

ÖZ

Amaç: Bu çalışmanın amacı serebral palsili (SP) çocuklarda fonksiyonellik, özür ve sağlığın tanımlanmasında İşlevsellik, Yeti Yitimi ve Sağlığın Uluslararası Sınıflandırması-Çocuklar ve Gençler (ICF-CY) versiyonunun kullanım etkinliğini incelemektir.

Yöntemler: Çalışmaya yaş ortalaması 9,13±2,2 yıl olan (6-13 yıl) 30 diplejik veya hemiplejik SP'li çocuk (13 kız; 17 erkek) katılmıştır. Oluşturulan ICF Kısa Set için SP'li çocuklarda sağlık ve fonksiyonelliğin tanımlanmasında en uygun olan 35 kategori seçilmiştir. Değerlendirmede ayrıca yürüme ve denge testleri, kaba motor fonksiyon ölçümü, Çocuklar İçin Bağımsızlık Ölçeği (Wee-FIM) ve Çocuk Sağlık Anketi-Anne/Baba Raporu da (CHQ-PF50) kullanılmıştır. Her bir çocuğun vücut yapısı ve fonksiyonu, aktivite ve katılımı ile çevresine ait kısıtlayıcı ve kolaylaştırıcı faktörleri kodlanmıştır.

Bulgular: Çalışmanın sonucunda ICF kısa set vücut fonksiyonları ve aktivite-katılım ile yürüme ve denge testleri, Kaba Motor Fonksiyon Ölçümü-88 (KMFÖ-88), Pediyatrik Fonksiyonel Bağımsızlık Ölçütü (PFBÖ) genel olarak orta düzeyde ilişki bulunmuştur ($p<0,05$). ICF kısa set vücut fonksiyonları ve aktivite-katılım ile CHQ- PF50 arasında zayıf-orta düzeyde ilişki bulunmuştur ($p<0,05$). ICF kısa set çevresel faktörler ile yürüme ve denge testleri, KMFÖ- 88, PFBÖ, CHQ- PF 50 arsında genel olarak zayıf düzeyde ilişki bulunmuştur ($p<0,05$).

Sonuç: Serebral palsili çocuklarda fonksiyon, özür ve sağlığın tanımlanmasında ICF'nin etkili bir kavramsal çerçeve olduğu, ICF sisteminin referans bir değerlendirme ölçütü olarak

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assessment criterion and that it will guide physiotherapists working with children with CP.

Keywords: Cerebral Palsy, ICF, motor activity, activity-participation

kullanılabileceğini ve SP'li çocuklarla çalışan fizyoterapistlere yol gösterici olacağını düşünmekteyiz.

Anahtar Sözcükler: Serebral palsi, ICF, motor aktivite, aktivite-katılım

Introduction

Cerebral palsy (CP) is defined as a group of motor disorder syndromes that develop secondary to brain anomalies or lesions that develop in the early stages of development and are not progressive, but often change (1,2).

The World Health Organization (WHO) gives the disability rate as 10%. Of disabled people, 80% live in low income countries. In our country-Turkey- the disability rate is 29%. The rate of disability is increasing in the world. The incidence of CP has been reported to be 1.5-2.5 per 1000 live births in many populations. In epidemiological studies conducted in Turkey, the frequency of CP has been reported as 4.4/1,000 (3). CP can affect the child's motor and sensory systems, as well as can cause many deformities and deficiencies. In parallel with these developments, it became necessary to establish a common language for functioning, disability and health classification.

In this context, international classification studies initiated by Philip Wood in 1973 for the first time in the USA have developed and reached its current level (4). The revisions continued over the years and in 1993 the Classification of Impairments, Disabilities and Handicaps System was published. In the 54th World Health Assembly, ICF (International Classification of Functioning, Disability and Health), which was a conceptual framework that assessed health and disability on an individual and social level, was formally structured with the participation of 191 member countries. ICF is an integrative holistic approach based on the bio-psycho-social model (5).

According to ICF system; there are Structural and Functional Disabilities Disorder (spasticity, muscle weakness, contracture joint movement limitation), Activity (inability to walk, stairs, difficulty eating), Participation (difficulty in going to school, not visiting friends, not going to the cinema), Personal factors (gender, age, education level, motivation), and Environmental Factors (physical environment, social environment, social security, economic conditions) (2).

A version of ICF used in children and youth (ICF-CY) with special content and additional details was developed to create a common language on functional and participation problems in children and young people (3,6,7). ICF-CY can be used to guide functional status assessment, goal achievement, treatment planning and control, as well as for classification and outcome measurements. Additional information provided by profiling the child's functionality within and between its components provides a more rational and more meaningful basis for identifying treatment needs, using resources, and evaluating outcomes through assessments based on ICF-CY (8,9).

The aim of this study is to determine the effectiveness of ICF System in children with diparetic or hemiparetic CP with different assessments and scales.

Methods

The study was carried out in Denizli Yağmur Çocukları Special Education and Rehabilitation Center between 01.01.2016-01.12.2016.

Participants

Thirty diplegic or hemiplegic children aged between 6-14 years living in Denizli were included in the study. As a result of the power analysis, the effect size of the correlation was assumed to be moderate and it was determined that it was sufficient to involve 26 people in the study in order to obtain 80% power with 95% confidence. For the study, approval was obtained from Pamukkale University Medical Ethics Committee with 16,733 number and 10.03.2016. It was also supported by the Scientific Research Projects Coordination Unit of Pamukkale University (2016SBE006). Informed consent forms were obtained from families of children with CP for the study.

Inclusion Criteria for Volunteers

- Children with CP aged between 6-14 years old
- Clinical type of diparetic and hemiparetic
- Children who can walk independently or using auxiliary devices
- Children who meet level I, II or III according to the GMFCS

Exclusion Criteria for Volunteers:

- The presence of a secondary disability other than CP
- Difficulty in communication and cooperation

Descriptive Data

A form was created in which the socio-demographic characteristics of the patients were recorded. This form also contained the data recording section of the tests and scales used during the evaluation phase.

Assessment Methods

ICF Core Set

Core ICF Set is used to describe the functional skills and difficulties that children with CP use to perform daily activities. Core ICF Set: body structures: 1 item, body functions: 10 items, activities and participation: 13 items, environmental factors: 11 items consisting of 35 ICF categories (10-14).

Gross Motor Function Measure (GMFM- 88)

The GMFM- 88 was used to determine functional skill level. GMFM- 88, which has 5 sub-dimensions, evaluates the child with CP in terms of lying-rolling (dimension A), sitting (dimension B), crawling-kneeling (dimension C), standing (dimension D) and walking activities (dimension E). It is a scale that measures the rate of performing activities. Accordingly, the multiplication of the maximum score of the patient's score in each dimension by 100 represents the percentage score obtained for that dimension. The total GMFM- 88 score is obtained by dividing the sum of the scores obtained from the dimensions by 5 (dimensions A-E). The higher the score, the higher the level of performance of gross motor skills of the patient with CP (15,16).

Balance Assessment Tests

Pediatric Berg Balance Scale (PBBS)

The Pediatric Berg Balance Scale (PBBS), a child version of the Berg Balance Scale, was developed by Franjoine et al. (17) The scale consists of 14 sections and each section is scored between 0-4. The highest score that can be obtained from the scale is 56. The higher the score, the higher the level of balance (17,18).

Minute Walking Test (1MWT)

Testing a child at maximum gait speed is considered to be a better assessment of the functional ability for dynamic balance, muscle performance and endurance compared to the gait speed of his/her choice, and may allow many children with CP to walk 1 minute. 1-Minute Walking Test (1MWT) is an easy-to-use, inexpensive functional ability assessment method in clinical trials when time constraints and other necessary testing procedures make it difficult to perform an overall functional assessment (19,20).

Pediatric Functional Independence Measure (WeeFIM)

Pediatric Functional Independence Measure (WeeFIM) was modeled from Functional Independence Measure (FIM), the FIM used as an adult rehabilitation assessment method. It is used to determine the level of functional independence of children and changes in time-dependent functions (21).

Child Health Survey-Mother/Father Report (CHQ-PF50)

It is one of the tests used in children with disabilities to evaluate the quality of life of children with CP. The Child Health Questionnaire-The Mother/Father Report (CHQ-PF50) is an assessment method developed to assess the health-related quality of life of children aged 5 to 18 years. The family version of the CHQ-PF50 was culturally adapted to ensure its validity in Turkish. The CHQ-PF50 consists of 14 subsections and contains a total of 50 question items. Measured concepts are: general health (GGH), physical function (PF), role/social constraints (RP) due to emotional or behavioral difficulties, role/social constraints due to physical health, pain and discomfort, behavior, mental health (MH), self-esteem (SE), general health perception (GH), emotional impact on the parent (PE), time effect on the parent, family activities, family adjustment. It also includes the section on change in health, which compares the health change in a child to a year earlier. The best total score that can be obtained from the departments is "100" and the worst score is "0… In this study, the scores obtained from all sub-sections were summed and the evaluations were made on the total score. Families were informed about the content of the survey. They were told about the expectations and asked to answer the questions in the survey (22).

Statistical Analysis

Data were analyzed by SPSS (21.0 version) package program. Continuous variables mean ± standard deviation, median (minimum-maximum values) and categorical variables are given as number (n) and percentage (%). Spearman Correlation Analysis was used to examine the relationships between the scales. Significance level was accepted as $p \leq 0.05$ (23).

Results

Thirty children with CP (14 hemiparesis, 16 diparesis) participated in the study. The mean age of the children was 9.13±2.21 years, the mean body weight was 31.43±11.37 kg, the average length was 132.73±15.86 cm, and the duration of treatment was 6.15±2.75 years (Table 1).

Table 2 shows the mean Gross Motor Function Measure-88 (GMFM-88) total score, WeeFIM total score, PBBS and 1MWT scores.

The average values of the CHQ-PF50 sections of the patients are shown in Table 3.

The relationships between PBBS total score, GMFM-88 total score, WeeFIM total score, 1MWT score and Body Function parameters are shown in Table 4.

There was a statistically significant negative correlation between PBBS, GMFM-88 and WeeFIM total scores and b134, b167 and motivation b1301 of mental related functions and b710 (Mobility functions of joints, easy movement of arms and legs), b735 (Muscle tone function, hypertonus or hypotonus) and b760 (Control of voluntary movement functions) parameters of neuromusculoskeletal and movement related functions.

There was a statistically significant negative correlation between 1MWT score and b134 in mental functions and b710, b735 and b760 in neuromusculoskeletal and movement related parameters.

The relationship between CHQ-PF50 and Body Function parameters are shown in Table 5.

The relationship between PBBS and GMFM-88 total score and ICF components Activities and Participation parameters (performance-capacity) are given in Table 6.

There was a statistically significant negative correlation between the total score of the WeeFIM and the 1MWT score, all of the Activity and Participation parameters (except the d530 of the WeeFIM and d175 of the 1MWT), which were components of the ICF ($p<0.05$) (Table 7 I-II).

The relationship between CHQ-PF50 and ICF components Activities and Participation (performance-capacity) is given in Table 8 I-II-III.

Table 1. Demographic and clinical characteristics of children with CP

Parameter	X ± SD	Median (min-max)
Age (year)	9.13±2.21	9 (6-13)
Height (cm)	132.73±15.86	131.5 (109-176)
Weight (kg)	31.43±11.37	29 (13-75)
Birth weight (kg)	2517.33±985.82	2750 (700-4,200)
Incubation time (weeks)	16.8±22.3	7.5 (0-90)
Rehabilitation time (years)	6.15±2.75	6 (1-12)
	n	%
Gender		
Girl	13	43
Boy	17	57
Delivery method		
Cesarean	19	63
Normal	11	37
Dominant hand		
Right	13	43
Left	17	57

X: Mean, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. GMFM-88, WeeFIM, PBBS and 1MWT scores

Parameter	X ± SD	Median (min-max)
GMFM-88-TS	80.46±20.51	89.8 (18.88-99.44)
WeeFIM-TS	101.63±26.75	113.5 (16-126)
PBBS-TS	38.4±20.51	50 (4-56)
1MWT (m)	45.87±20.72	48 (2-80)

GMFM-88-TS: GMFM-88 total score, WeeFIM-TS: WeeFIM total score, PBBS- TS: PBBS total score, 1MWT: 1-Minute Walking Test, X: Mean, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 3. CHQ-PF 50 scores

CHQ-PF 50	X ± SD	Median (min-max)
GGH	45±18.89	46.0 (0-60)
PF	48.75±36.36	46.80 (0-100)
REB	49.25±37.33	41.97 (0-100)
RP	48.30±39.94	45.83 (0-100)
BP	70.00±25.99	75.71 (20-100)
BE	67.54±23.52	69.44 (0-100)
GBE	51.00±32.86	52.50 (0-100)
MH	61.83±20.73	60.71 (15-95)
SE	64.71±20.31	69.99 (0-100)
GH	43.74±16.04	42.70 (13.3-76.6)
PE	39.22±21.83	40.38 (0-75)
PT	48.14±34.19	48.14 (0-100)
FA	61.27±23.29	64.28 (8.3-100)
FC	68.83±24.76	72.50 (0-100)

X: Mean, SD: Standard deviation, Min: Minimum, Max: Maximum
GGH: General health, PF: Physical function, REB: Emotional or behavioral difficulties due to role/social restrictions, RP: Physical health role/social restrictions, BP: Pain and discomfort, BE: Behavior, MH: Mental health, SE: Self-esteem, GH: General health perception, PE: Emotional effect on parents, PT: Time effect on parents, FA: Family activities, FC: Family adjustment, GBE: Global behavior

The relationship between GMFM-88-TS, WeeFIM-TS, PBBS and 1MWT score and Environmental Factors from ICF Components is shown in Table 9.

There was a statistically significant negative (facilitating) relationship between PBBS score, GMFM-88 total score and 1MWT and e150 parameter from Environmental Factors ($p<0.05$).

There was a statistically significant negative (facilitating) relationship between WeeFIM total score and e150, e460 and e580 parameters of Environmental Factors ($p<0.05$).

The relationship between the parameters of CHQ-PF50 and Environmental Factors from ICF Components is shown in Table 10.

Discussion

The ICF coding system provides a framework for measuring, classifying and conceptualizing the disability and functioning. It aims to create a common and standard language for defining health and health-related situations (24). In this study, which was initiated in 1973, WHO requested that the concepts of impairment, disability and handicap be dealt with in a multidimensional way. These steps paved the way for the ICF classification system, which led to an international dimension by spreading the issue (3,25).

In recent years, the bio-psychosocial system, which advocates that individuals with permanent or temporary disability or handicap should be examined with a holistic point of view as well as their medical conditions, has advocated the establishment of new registration and identification systems. In this context, ICF-CY systems have been developed in the last 15 years. International classification studies initiated by Philip Wood in 1973 for the first time in the USA have developed and reached their present level. The first studies on this issue in Turkey were initiated by the Administration of Disabled People. In the first step studies, the Turkish translation of ICF was made (25).

Participation is defined by the International Classification of Functioning, Disability and Health (ICF) as "in-volvement in a life situation" and encompasses, amongothers, the domains: domestic life, education and employ-ment, interpersonal interactions and relationships, and community, social, and civic life. According to the ICF, participation performance can be qualified objectively by the experi-enced difficulty or the use of assistive devices for human assistance needed in performing life habits (3).

The results of this study, which was planned to demonstrate the effectiveness of ICF in children with CP, by correlating them with different tests and scales, showed that ICF sub-components could be used to identify problems of children with CP, determine activity and participation levels, and determine the impact of environmental factors.

In their systematic review of adults with CP using the International Classification of Functioning, Disability and Health,(26) identified the most commonly used results in studies of adults with CP. The most common ones were pain, mobility, self-care, employment, and recreation. It has been stated that the broad ICF categories defined in this study emphasize the heterogeneity of functionality and disability in adults with CP. However, it was stated that there was a limited focus on environmental and personal factors.

Children's participation in various activities during the daytime is important for their development. Participation in activities is known to increase children's creativity and to integrate them into social life where they develop their skills. Physiotherapy and occupational therapy are applied to children with CP for a long time in order to increase their mobility and to gain independence in self-care, school, play and leisure activities. According to Pihlar (27), occupational therapy should be within the framework of multiple sources, theories and models and should include many functions. In parallel with this idea of Pihlar (27), ICF has been considered to evaluate the individual from a multifaceted perspective.

Hurley et al. (28), in their studies examining how generalized data obtained from CP records can be generalized in order to fully understand CP, they emphasized that the kept records contain important information about how CP affects the person, family and society. Also; they stated that the rate of record keeping increased, the cost decreased and the transfer of information between the researcher, the individual and the society became easier thanks to technological developments. In a study examining the status of reflecting physiotherapy goals of the two most commonly used scales [GMFM-88 and Pediatric Evaluation of Disability Inventory (PEDI)] to evaluate the disability status of children with CP, it was seen that the individual goals determined in the children's physiotherapy program were met by the activities in these scales.

Table 4. Relationship between Body Functions and PBBS, GMFM, WeeFIM and 1MWT

Body functions											
		b117	b1301	b134	b140	b167	b210	b280	b710	b735	b760
PBBS-TS	r	-0.289	-0.428*	-0.492**	-0.044	-0.500**	0.145	-0.077	-0.756**	-0.496**	-0.765**
	p	0.121	0.018	0.006	0.817	0.005	0.444	0.685	0.000	0.005	0.000
GMFM- 88-TS	r	-0.403*	-0.427*	-0.406*	-0.105	-0.405*	0.005	0.058	-0.790**	-0.542**	-0.720**
	p	0.027	0.019	0.026	0.580	0.026	0.980	0.762	0.000	0.002	0.000
WeeFIM-TS	r	-0.439*	-0.578**	-0.609**	-0.293	-0.419*	-0.044	-0.039	-0.737**	-0.603**	-0.819**
	p	0.015	0.0001	0.000	0.116	0.021	0.816	0.840	0.000	0.000	0.000
1MWT(m)	r	-0.216	-0.336	-0.498**	-0.275	-0.241	0.085	0.310	-0.513**	-0.409*	-0.592**
	p	0.253	0.069	0.005	0.141	0.200	0.656	0.096	0.004	0.025	0.001

GMFM-88-TS: GMFM-88 total score, WeeFIM-TS: WeeFIM total score, PBBS- TS: PBBS Total Score, 1MWT: 1-Minute Walking Test, *p<0.05, **p<0.01

Table 5. Relationship between CHQ-PF50 and body functions

Body functions										
CHQ- PF 50	**b117**	**b1301**	**b134**	**b140**	**b167**	**b210**	**b280**	**b710**	**b735**	**b760**
r	,111	.102	,163	-.022	.234	-.046	.080	-.070	.160	.068
GGH										
p	.558	.590	.389	.906	.214	.811	.672	.712	.399	.721
r	-.411*	-.456*	-,360	-.220	-.363*	-.183	-.097	-.696**	-.315	-.568**
PF										
p	.024	.011	.051	.242	.049	.334	.610	.000	.090	.001
r	-.489**	-.664**	-.513**	-.112	-.365*	.033	-.170	-.661**	-.148	-.427*
REB										
p	.006	.000	.004	.555	.047	.862	.369	.000	.434	.018
r	-.411*	-.600**	-.437*	-.064	-.371*	.113	-.145	-.581**	-.083	-.377*
RP										
p	.024	.000	.016	.738	.044	.554	.444	.001	.664	.040
r	-.278	-.424*	-.413*	-.235	-.307	.337	-.195	-.246	.167	-.056
BP										
p	.136	.020	.023	.211	.099	.069	.302	.190	.377	.768
r	-.424*	-.461*	-.457*	-.423*	-.353	.087	-,238	-.211	.071	-.117
BE										
p	.020	.010	.011	.020	.056	.648	.205	.263	.711	.538
r	-.254	-.414*	-.451*	-.273	-.419*	-.008	-.132	-.314	-.100	-.389*
GBE										
p	.175	.023	.012	.145	.021	.964	.488	.091	.600	.034
r	-.543**	-.607**	-.659**	-.560**	-.525**	.403*	-.316	-.370*	-.173	-.287
MH										
p	.002	.000	.000	.001	.003	.027	.089	.044	.361	.124
r	-.468**	-.573**	-.536**	-,295	-.510**	.331	-.273	-.416*	-.061	-.306
SE										
p	.009	.001	.002	.114	.004	.074	.145	.022	.748	.101
r	.043	-.004	.011	.074	-.086	-.064	.270	-.133	-.162	-377*
GH										
p	.820	.982	.955	.698	.650	.735	.149	.483	.393	.040
r	.067	.040	-.109	-.077	-.103	.097	.099	-.120	.085	-.140
PE										
p	.731	.837	.573	.693	.596	.615	.609	.536	.662	.470
r	-.137	-.174	-.190	.025	-.237	-.097	-.130	-.300	-.066	-.324
PT										
p	.470	.358	.315	.898	.206	.611	.495	.107	.731	.080
r	-.312	-.414*	-.388*	-.321	-.403*	-.085	-.206	-.320	-.107	-.354
FA										
p	.093	.023	.034	.084	.027	.657	.274	.084	.574	.055
r	-.099	-.157	-.359	-.206	-.227	.127	-.225	-.049	.007	-.126
FC										
p	.602	.408	.052	.274	.227	.502	.233	.795	.972	.507

*p<0.05, **p<0.01, r: Correlation coefficient, GGH: General health, PF: Physical function, REB: Emotional or behavioral difficulties due to role/social restrictions, RP: Physical health role/social restrictions, BP: Pain and discomfort, BE: Behavior, MH: Mental health, SE: Self-esteem, GH: General health perception, PE: Emotional effect on parents, PT: Time effect on parents, FA: Family activities, FC: Family adjustment, GBE: Global behavior

The work of Engelen et al. (29) supports the ICF as an important source of information collection.

In a systematic review examining the studies using the ICF-CY coding system to compare and identify the most frequently mentioned functional areas of outcome measures used for children with CP, 161 systematic categories associated with ICF-CY were found. Of the 161 categories, 53 (33.5%) were associated with body functions, 75 (46%) activity/participation, 26 (16.1%) environmental factors, and 7 (4.3%) related to body structures. The content of outcome measures selected for use in clinical practice and studies in children with CP is important in guiding the clinician and the researcher (13).

Jeglinsky et al. (30) included 70 children between the ages of 1-16 with CP, and stated that there were some deficiencies in determining the relationship between children's needs, functional deficiencies and treatment goals. They therefore emphasize the need to develop basic ICF-CY subgroups that can serve as a framework to help identify the needs of the child and the needs of professionals and parents.

Table 6 I-II. Relationship between activity-participation and PBBS and GMFM-88 scores

I		d175 p	d175 c	d230 p	d230 c	d350 p	d350 c	d415 p	d415 c	d440 p	d440 c	d450 p	d450 c	d460 p	d460 c
PBBS-TS	**r**	-.398*	-.350	-.696**	-.692**	-.456*	-.442*	-.693**	-.657**	-.573**	-.590**	-.817**	-.786**	-.807**	-.814**
	p	.030	.058	.000	.000	.011	.015	.000	.000	.001	.001	.000	.000	.000	.000
GMFM-TS	**r**	-.389*	-.309	-.653**	-.623**	-.430*	-.358	-.764**	-.654**	-.685**	-.643**	-.740**	-.687**	-.749**	-.719**
	p	.034	.097	.000	.000	.018	.052	.000	.000	.000	.000	.000	.000	.000	.000

II		d530 p	d530 c	d550 p	d550 c	d710 p	d710 c	d760 p	d760 c	d820 p	d820 c	d920 p	d920 c
PBBS-TS	**r**	-.664**	-.638**	-.598**	-.572**	-.460*	-.441*	-.504**	-.461*	-.692**	-.692**	-.776**	-.724**
	p	.000	.000	.000	.001	.011	.015	.004	.010	.000	.000	.000	.000
GMFM-TS	**r**	-.661**	-.598**	-.540**	-.490**	-.392*	-.358	-.426*	-.334	-.638**	-.610**	-.695**	-.663**
	p	.000	.000	.002	.006	.032	.052	.019	.071	.000	.000	.000	.000

*p<0,05, **p<0,01, p: Performance, k: Capacity, r: Correlation Coefficient, GMFM-88-TS: GMFM-88 Total Score, PBBS- TS: PBBS Total Score, **Activity-Participation Parameters:** d175: Problem solving, d230: Performing daily routines, d350: Conversation, d415: Maintaining body position, d440: Fine hand skills, d450: Walking, d460: Walking around, d530: Toilet, d550: Eating, d710 : Basic interpersonal interactions, d760: Family relations, s820: School education, d920: Fun and leisure

Table 7 I-II. Relationship between Activity-Participation and Wee-FIM and 1MWT scores

I		d175 p	d175 c	d230 p	d230 c	d350 p	d350 c	d415 p	d415 c	d440 p	d440 c	d450 p	d450 c	d460 p
WeeFIM-TS	**r**	-.541**	-.491**	-.871**	-.824**	-.584**	-.556**	-.716**	-.624**	-.740**	-.691**	-.830**	-.781**	-.831**
	p	.002	.006	.000	.000	.001	.001	.000	.000	.000	.000	.000	.000	.000
1MWT	**r**	-.337	-.274	-.687**	-.619**	-.440*	-.340	-.630**	-.447*	-.499**	-.381*	-.628**	-.557**	-.685**
	p	.068	.143	.000	.000	.015	.066	.000	.013	.005	.038	.000	.001	.000

II		d460 c	d530 p	d530 c	d550 p	d550 c	d710 p	d710 c	d760 p	d760 c	d820 p	d820 c	d920 p	d920 c
WeeFIM-TS	**r**	-,.819**	-.819**	-.760**	-.695**	-.652**	-.524**	-.489**	-.565**	-.444*	-.757**	-.743**	-.856**	-.822**
	p	.000	.000	.000	.000	.000	.003	.006	.001	.014	.000	.000	.000	.000
1MWT	**r**	-.615**	-.643**	-.570**	-.469**	-.392*	-.353	-.304	-.330	-.169	-.764**	-.697**	-.755**	-.695**
	p	.000	.000	.001	.009	..032	.055	.102	.074	.373	.000	.000	.000	.000

*p<0.05, **p<0.01, p: Performance, k: Capacity, r: Correlation Coefficient, WeeFIM-TS: WeeFIM Total Score, 1MWT: 1-Minute Walking Test, **Activity-Participation Parameters:** d175: Problem solving, d230: Performing daily routines, d350: Conversation, d415: Maintaining body position, d440: Fine hand skills, d450: Walking, d460: Walking around, d530: Toilet, d550: Eating, d710 : Basic interpersonal interactions, d760: Family relations, s820: School education, d920: Fun and leisure

Ogonowski et al. (31) examined the compatibility of ICF coding system between the evaluators in children with disabilities and included 60 children from different disability groups. In the ICF coding of children, 40 parameters were evaluated by coding the sub-components of learning and applying knowledge and activities, general tasks and demands, communication, displacement, self-care, interpersonal interaction and relations from activity and participation component. PEDI, Vineland Behavior Scale, School Achievement Scale were used together with ICF coding. As a result of ICF coding, the agreement between the evaluators was found to be low in general tasks and demands, interpersonal interaction and relationships, learning and knowledge application, communication, displacement, and high level of self-care. There was a positive correlation between PEDI and ICF codes, but no correlation was found between the Vineland Behavior Scale, School Achievement Scale and ICF codes.

Cerebral palsy is a heterogeneous condition with different clinical outcomes and potential disorders (32). This diversity is likely to be reflected in the evaluation choices used in studies conducted with children with CP. In a systematic review, it was seen that the ICF-CY scopes of the measurements used in the studies reflected CP diversity in the study and clinical applications (33).

Core sets also promote multidisciplinary cooperation by encouraging all members of the team to use the same language "ICF-CY" classes in the definition of function in children with CP (34).

In their studies on the application of ICF-CY in the evaluation of rehabilitation of patients with CP; Tomás et al (35). expressed the need for a systematic approach to CP rehabilitation and the importance of dynamic evaluation of the results. They stated that ICF-CY could be used to define and measure the extent of health disorders in children with CP, but there were no clear quantitative criteria that allowed the use of ICF-CY to determine the effectiveness of medical rehabilitation of patients with CP. In addition to general physical and clinical neurological examinations in various 29 children with CP who received medical

Table 8 I-II. Relationship between Activity-Participation and CHQ-PF50

I		d175 p	d175 c	d230 p	d230 c	d350 p	d350 c	d415 p	d415 c	d440 p	d440 c	d450 p	d450 c	d460 p	d460 c
GGH	r	.222	.205	.081	.110	.212	.214	-.065	-.005	.146	.175	.195	.172	.221	.228
	p	.239	.278	.672	.564	.261	.256	.733	.978	.442	.355	.301	.364	.241	.226
PF	r	-.468**	-.396*	-.581**	-.536**	-.460*	-.445*	-.622**	-.528**	-.519**	-.519**	-.566**	-.561**	-.563**	-.563**
	p	.009	.030	.001	.002	.011	.014	.000	.003	.003	.003	.001	.001	.001	.001
REB	r	-.370*	-.330	-.483**	-.551**	-.359	-.386*	-.477**	-.420*	-.424*	-.461*	-.459*	-.490**	-.494**	-.484**
	p	.044	.075	.007	.002	.051	.035	.008	.021	.020	.010	.011	.006	.005	.007
RP	r	-.311	-.271	-.383*	-.450*	-.335	-.357	-.394*	-.336	-.279	-.333	-.367*	-.395*	-.413*	-.395*
	p	.094	.147	.037	.013	.071	.053	.031	.070	.136	.072	.046	.031	.023	.031
BP	r	-.310	-.274	-.265	-.365*	-.231	-.269	-.108	-.090	.108	.038	-.130	-.156	-.161	-.152
	p	.096	.143	.156	.047	.219	.151	.569	.635	.569	.842	.494	.411	.395	.424
BE	r	-.414*	-.377*	-.186	-.264	-.300	-.373*	-.273	-.321	-.057	-.126	-.150	-.199	-.134	-.182
	p	.023	.040	.324	.158	.108	.043	.145	.084	.766	.507	.429	.293	.481	.335
GBE	r	-.433*	-.390*	-.376*	-.365*	-.414*	-.445*	-.411*	-.417*	-.189	-.233	-.408*	-.416*	-.378*	-.419*
	p	.017	.033	.041	.047	.023	.014	.024	.022	.318	.215	.025	.022	.039	.021
MH	r	-.588**	-.622**	-.460*	-.578**	-.475**	-.538**	-.445*	-.483**	-.264	-.301	-.394*	-.419*	-.401*	-.433*
	p	.001	.000	.011	.001	.008	.002	.014	.007	.159	.106	.031	.021	.028	.017
SE	r	-.372*	-.346	-.303	-.416*	-.326	-.400*	-.388*	-.457*	-.114	-.216	-.305	-.332	-.272	-.318
	p	.043	.061	.104	.022	.079	.029	.034	.011	.550	.252	.101	.073	.146	.087
GH	r	-.076	-.015	-.127	-.069	-.105	-.077	-.145	-.130	-.130	-.126	-.177	-.139	-.181	-.168
	p	.692	.938	.502	.718	.579	.687	.446	.493	.494	.506	.350	.462	.338	.376
PE	r	-.183	-.121	-.179	-.066	-.274	-.194	-.139	.015	.050	.079	-.098	-.070	-.138	-.116
	p	.342	.532	.353	.734	.150	.313	.473	.940	.799	.684	.614	.720	.476	.550
PT	r	-.213	-.139	-101	-.073	-.299	-.282	-.204	-.171	-.056	-.140	-.206	-.220	-.189	-.211
	p	.259	.465	.594	.700	.108	.131	.281	.367	.767	.462	.276	.243	.316	.264
FA	r	-.494**	-.432*	-.444*	-.418*	-.515**	-.520**	-.334	-.301	-.265	-.349	-.416*	-.426*	-.353	-.390*
	p	.005	.017	.014	.021	.004	.003	.071	.106	.156	.059	.022	.019	.056	.033
FC	r	-.243	-.195	-.249	-.263	-.215	-.231	-.204	-.242	.001	-.080	-.235	-.245	-.196	-.216
	p	.196	.302	.184	.161	.255	.219	.279	.198	.996	.675	.211	.192	.299	.252

II		d530 p	d530 c	d550 p	d550 c	d710 p	d710 c	d760 p	d760 c	d820 p	d820 c	d920 p	d920 c
GGH	r	.195	.176	.103	.104	.206	.162	.191	.154	.108	.086	.092	.090
	p	.301	.352	.587	.585	.275	.391	.312	.416	.571	.651	.628	.636
PF	r	-.629**	-.610**	-.582**	-.561**	-.440*	-.453*	-.438*	-.352	-.464**	-.472**	-.520**	-.549**
	p	.000	.000	.001	.001	.015	.012	.015	.056	.010	.008	.003	.002
REB	r	-.471**	-.508**	-.408*	-.406*	-.390*	-.435*	-.349	-.285	-.544**	-.546**	-.506**	-.569**
	p	.009	.004	.025	.026	.033	.016	.059	.127	.002	.002	.004	.001
RP	r	-.384*	-.427*	-.385*	-.383*	-.378*	-.423*	-.340	-.269	-.455*	-.455*	-.400*	-.434*
	p	.036	.018	.036	.037	.039	.020	.066	.151	.012	.011	.029	.017
BP	r	-.271	-.269	-.288	-.300	-.322	-.369*	-.293	-.264	-.307	-.334	-.222	-.327
	p	.148	.151	.123	.107	.083	.045	.117	.158	.099	.071	.239	.078
BE	r	-.267	-.320	-.313	-.361*	-.377*	-.427*	-.393*	-.383*	-.235	-.298	-.133	-.284
	p	.155	.084	.092	.050	.040	.019	.032	.036	.211	.110	.484	.128
GBE	r	-.393*	-.390*	-.341	-.353	-.410*	-.410*	-.419*	-.409*	-.465**	-.509**	-.401*	-.504**
	p	.032	.033	.065	.056	.024	.025	.021	.025	.010	.004	.028	.005
MH	r	-.542**	-.578**	-.581**	-.616**	-.599**	-.642**	-.608**	-.583**	-.572**	-.612**	-.469**	-.590**
	p	.002	.001	.001	.000	.000	.000	.000	.001	.001	.000	.009	.001
SE	r	-.310	-.349	-.412*	-.451*	-.430*	-.465**	-.488**	-.529**	-.366*	-.432*	-.314	-.391*
	p	.096	.058	.024	.012	.018	.010	.006	.003	.047	.017	.091	.033
GH	r	-.084	,024	-.049	-.018	-.044	.002	-.118	-.111	-.060	-.051	-.056	-.051
	p	.659	.901	.797	.924	.818	.993	.536	.561	.753	.788	.770	.787
PE	r	-.213	-.122	-.158	-.125	-.145	-.121	-.090	.069	-.212	-.173	-.190	-.209
	p	.268	.529	.412	.517	.454	.532	.644	.722	.269	.368	.325	.276
PT	r	-.203	-.144	-.117	-.122	-.241	-.241	-.182	-.124	-.173	-.186	-.136	-.166
	p	.281	.448	.539	.519	.199	.200	.337	.513	.361	.326	.475	.380
FA	r	-.477**	-.411*	-.320	-.328	-.408*	-.405*	-.442*	-.370*	-.402*	-.431*	-.377*	-.482**
	p	.008	.024	.085	.076	.025	.026	.015	.044	.028	.017	.040	.007
FC	r	-.235	-.154	-.116	-.138	-.195	-.181	-.235	-.204	-.246	-.285	-.195	-.276
	p	.212	.416	.542	.467	.303	.337	.212	.280	.189	.127	.301	.139

*p<0,05, **p<0,01, p: Performance, k: Capacity, r: Correlation Coefficient, **Activity-Participation Parameters:** d175: Problem solving, d230: Performing daily routines, d350: Conversation, d415: Maintaining body position, d440: Fine hand skills, d450: Walking, d460: Walking around, d530: Toilet, d550: Eating, d710 : Basic interpersonal interactions, d760: Family relations, s820: School education, d920: Fun and leisure, GGH: General health, PF: Physical function, REB: Role Social Restrictions Due to Emotional or Behavioral Difficulties, RP: Role Social Restrictions Due to Physical Health, BP: Pain and Unreliability, BE: Behavior, MH: Mental health, SE: Self-Esteem , GH: General Health Perception, PE: Emotional effect on parent, PT: Time effect on parent, FA: Family activities, FC: Family compliance

Table 9. Relationship between GMFM-88, WeeFIM, PBS and 1MWT scores

		e115	e120	e125	e130	e140	e150	e310	e320	e460	e580	e585
PBS	r	-.117	-.359	-.062	-.131	-.146	-.516**	-.223	-.262	-.340	-.312	-.174
	p	-.539	.051	.745	.490	.440	.004	.237	.163	.066	.093	.359
GMFM	r	-.253	-.406*	-.018	-.082	-.203	-.603**	-.195	-.299	-.353	-.290	-.168
	p	.178	.026	.926	.667	.281	.000	.301	.108	.056	.121	.376
Wee-FIM	r	-.115	-.226	-.048	-.045	-.149	-.396*	-.136	-.204	-.433*	-.413*	-.325
	p	.545	.229	.802	.812	.433	.030	.475	.281	.017	.023	.079
1MWT	r	-.144	-.200	.216	.156	-.040	-.365*	.008	-.092	-.218	-.139	-.078
	p	.448	.290	.251	.409	.835	.047	.967	.630	.248	.464	.681

*p<0.05, **p<0.01, r: Correlation coefficient, Environmental Factors; e115: Products and technology for personal use in everyday life, e120: Products and technology for personal use in movement and transport, e125: Products and technology for communication, e130: Products and technology for education, e140: Culture, entertainment and sports e150: Design of public buildings, building and construction products and technology, e310: Close family, e320: Friends, e460: Social attitude, e580: Health care, systems and policies, e585: Education and training services, systems and policies.
GGH: General Health, PF: Physical Function, REB: Role Social Restrictions Due to Emotional or Behavioral Difficulties, RP: Role Social Restrictions Due to Physical Health, BP: Pain and unreliability, BE: Behavior, MH: Mental health, SE: Self-Esteem, GH: General health perception, PE: Emotional effect on parent, PT: Time effect on parent, FA: Family activities, FC: Family compliance

Table 10. Relationship between Environmental Factors and CHQ-PF50

CHQ- PF 50		e115	e120	e125	e130	e140	e150	e310	e320	e460	e580	e585
GGH	r	-,040	-,064	-,212	-,208	-,126	-,130	-,082	-,035	-,023	-,139	-,164
	p	,833	,736	,261	,271	,508	,494	,668	,855	,904	,464	,386
PF	r	-,035	-,162	,030	-,004	-,036	**-,454***	-,223	-,233	**-,456***	**-,494****	-,353
	p	,852	,392	,875	,985	,850	,012	,237	,215	,011	,005	,056
REB	r	,026	**-,414***	,047	,047	-,029	**-,524****	,014	-,058	-,311	-,279	-,104
	p	,891	,023	,805	,804	,878	,003	,940	,759	,095	,135	,585
RP	r	-,053	**-,505****	-,053	-,038	-,128	**-,617****	-,113	-,159	-,290	-,257	-,069
	p	,780	,004	,779	,841	,501	,000	,551	,403	,120	,170	,717
BP	r	,158	-,057	,155	,244	,031	-,210	,098	,106	-,158	-,147	,028
	p	,405	,763	,414	,194	,870	,265	,605	,576	,405	,439	,885
BE	r	,251	,045	,307	**,393***	,303	-,066	,034	,168	,073	-,089	-,043
	p	,180	,815	,099	,031	,104	,731	,860	,375	,701	,641	,822
GBE	r	-,020	-,235	,000	,003	-,005	-,341	-,224	-,134	-,304	**-,408***	-,355
	p	,919	,211	,998	,989	,980	,065	,235	,479	,103	,025	,054
MH	r	**,515****	,179	**,441***	**,534****	**,422***	-,016	,193	,259	,090	-,034	,045
	p	,004	,345	,015	,002	,020	,932	,308	,167	,636	,857	,815
SE	r	,133	-,122	,026	,169	,097	-,181	,034	,132	-,111	-,234	-,119
	p	,482	,519	,893	,371	,611	,338	,857	,488	,560	,214	,530
GH	r	**-,444***	**-,453***	-,177	-,282	-,256	**-,461***	**-,484****	**-,413***	-,247	-,134	-,150
	p	,014	,012	,350	,131	,171	,010	,007	,023	,188	,482	,427
PE	r	-,005	-,147	,167	,061	-,042	-,284	-,148	-,233	-,022	,031	,153
	p	,980	,446	,386	,755	,829	,135	,443	,223	,911	,875	,429
PT	r	,045	-,232	-,014	-,022	-,102	-,281	-,113	-,132	-,147	-,125	,038
	p	,814	,218	,941	,909	,593	,133	,554	,486	,439	,512	,842
FA	r	,116	-,008	,171	,150	,007	-,181	-,102	-,096	-,234	-,257	-,078
	p	,541	,968	,367	,428	,971	,338	,591	,612	,214	,170	,681
FC	r	,205	-,003	,083	,173	,029	-,001	,079	,060	,005	,037	,139
	p	,277	,989	,663	,359	,878	,996	,678	,755	,980	,846	,465

Environmental Factors; e115: Products and technology for personal use in everyday life, e120: Products and technology for personal use in movement and transport, e125: Products and technology for communication, e130: Products and technology for education, e140: Culture, entertainment and sports e150: Design of public buildings, building and construction products and technology, e310: Close family, e320: Friends, e460: Social attitude, e580: Health care, systems and policies, e585: Education and training services, systems and policies.
GGH: General Health, PF: Physical Function, REB: Role Social Restrictions Due to Emotional or Behavioral Difficulties, RP: Role Social Restrictions Due to Physical Health, BP: Pain and Unreliability, BE: Behavior, MH: Mental health, SE: Self-Esteem , GH: General health perception, PE: Emotional effect on parent, PT: Time effect on parent, FA: Family activities, FC: Family compliance

rehabilitation in hospital and outpatient clinics for 12 months in their study, all patients were tested using special questionnaires and scales before and after rehabilitation treatment, and also a brief ICF -CY core set. As a result, they suggested that the sensitivity of ICF-CY use to evaluate the effectiveness of medical rehabilitation of patients with CP was 89% and the specificity was 91% and it could be used to evaluate the effectiveness of medical rehabilitation.

When the effects of different treatment techniques were examined, ICF model showed that it provided a good model for measuring the effects of different physiotherapy techniques for CP (33).

Mutlu et al. (36) evaluated 448 children with CP ranging in age from 4 to 15 years. Children's performance test was evaluated using GMFM-88 and Manual Ability Classification System (MACS). In this study, ICF was used to evaluate activity limitations. Overall agreement of GMFM-88 and MACS with ICF was found to be 41%. Spastic children's compliance rate was 42%, 40% in dyskinetic children, 50% in ataxic children and 28% in mixed type children. They reported that ICF was an easy-to-use and fast classification tool for identifying activity limitations in children with CP.

In the above-mentioned studies, ICF coding system was found to be effective in determining the conditions of children with CP and young people with different disabilities and disabilities. In our study, a core set covering all sub-parameters of ICF-CY was used in parallel with the literature and a moderate agreement was found between the other tests and measurements used.

Although the studies agreed on some parts of the function, each study used its own classification set. In addition, the fact that each perspective emphasizes or prioritizes different areas of function has shown the importance of the coexistence of health care workers and families in the discussion of functional goals and in planning goal-oriented approaches. Therefore, ICF is not a classification and identification system that should be used only by health professionals. In order to improve the quality of life for disabled and handicapped people, other disciplines should also make training in this field.

In our study, the ICF core set for children with CP was found to be appropriate for the disability levels of the children evaluated and was compatible with the results of other selected evaluation tests and scales. In addition, the medium-level significant correlation between ICF results and the results of other selected tests and scales showed that ICF was effective in level definition of children with CP and its results were clinically important. The data obtained at the end of our study confirmed the hypothesis that performing ICF-CY in children with CP (Diparetic and Hemiparetic)is effective. Because all the results were compared with the results of previous studies and published studies, it was observed that there were parallel ideas.

Although our study was a cross-sectional study, the limitations of the study were that it was conducted with a small number of disabled children and that children with hemiparetic and diparetic CP were included in the study. Despite this, it yielded important results in terms of applicability of the ICF short set chosen in defining the functionality of children with CP. The strength of our study was that the validity and reliability of the tests and scales used in our study and associated with the ICF short set were determined.

In the light of our findings, the results of our study can be summarized as follows: The ICF core set for children with CP was found to be appropriate for the disability levels of the children evaluated and consistent with the results of other selected tests and scales.

In our study, a moderate relationship was found between the ICF core-set body functions and activity participation parameters and the assessment scales used in children with CP (walking, balance, GMFM-88, PBBS and CHQ-PF50, Wee FIM tests). A weak correlation was found between ICF core-set environmental factors and gait, balance, GMFM-88, PBBS and CHQ-PF50 tests.

The concordance of other test and scale results selected with the ICF core set for children with CP showed that the ICF system could be used as a reference evaluation criterion.

Conclusion

As a result, it is important that other tests and scales to be used with the ICF core set are selected in accordance with the ICF sub-parameters. The core set of ICF system is thought to be a guide for physiotherapists who work with children with CP especially in the field of pediatric rehabilitation in terms of evaluating body functions, activity-participation levels and environmental factors of children with CP in the ages between 6 and 14 years.

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Ethics

Ethics Committee Approval: For the study, approval was obtained from Pamukkale University Medical Ethics Committee with 16,733 number and 10.03.2016. It was also supported by the Scientific Research Projects Coordination Unit of Pamukkale University (2016SBE006).

Informed Consent: A consent form was completed by all participants.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: E.K., Design: U.C., E.K., Data Collection or Processing: A.H.A.S., E.K., Analysis or Interpretation: A.H.A.S., U.C., E.K., Literature Search: A.H.A.S., U.C., E.K., Writing: A.H.A.S., U.C., E.K.

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References

1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M. Definition and classification document. The definition and classification of cerebral palsy. Dev Med Child Neurol 2007;49:1-44.
2. Elbasan B, Türker D. Serebral Palside Fizyoterapi Rehabilitasyon. Pediatrik Fizyoterapi Rehabilitasyon, Elbasan B (Ed.) İstanbul Tip Kitabevleri. İstanbul 2016;87-123.
3. World Health Organization: International Classification of Functioning, Disability and Health (ICF). Geneva, Switzerland, World Health Organization 2001.
4. Kostanjsek N, Badley E, De Kleijn M, Ustun B. 'A man's reach should exceed his grasp Inmemory of professor Philip Wood. Disabil Rehabil 2009;31:1389-91.
5. Engel G. The clinical application of the biopsychosocial model. Am J Psychiatr 1980;137:535-44.
6. Adofsson M. Applying the ICF-CY to identify every day life situations of children and youth with disabilities. Jönköping: Doctorate Thesis, Jönköping Üni. 2011.
7. Ibragimova NK, Pless M, Adllfsln M, Granlund, M. and Akesson E. Using content analysis to link texts on assesment and intervention to the International Classification of Functioning, Disability and Health-version for children and youth (ICF-CY). Journal of Rehabilitation Medicine 2011;43,728-33.
8. Björck Akesson E, Wilder J, Granlund M, Pless M, Simeonsson R, Adllfson M, et al. The International Classification of Functioning, Disability and Health and the version for children and youth as a tool in child habilitation/early childhood intervention--feasibility and usefulness as a common language and frame of reference for practice. Disabil Rehabil 2010;32 suppl1:125-38.
9. Simeonsson RJ, Sauer-lee A, Grenlund M, Byörch-Ahesson E. "Developmental and health assessment in rehabilitation with the ICF for children and youth". Rehabilitation and Health Assessment: Applying ICF Guidelines, Mpofu E, Oklend T, Springer Pub. Company, New York, 2010;27-46.
10. Bickenbach J, Cieza A, Rauch A, Stucki G, editors. ICF Core Sets: Manual for Clinical Practice. Gottingen: Hogrefe, 2012.
11. Koutsogeorgou E, Quintas R, Raggi A, Bucciarelli P, Cerniauskaite M, Leonardi M. Linking courage in Europe built environment instrument tothe International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY). Maturitas 2012;73:218-24.
12. Huang CY, Tseng MH, Chen KL, Shieh JY, Lu L. Determinants of school activity performance in children with cerebral palsy: a multi dimensional approach using the ICF-CY as a framework. Res Dev Disabil 2013;34:4025-33.
13. Schiariti V, Klassen AF , Cieza A, Sauve K, O'Donnell M , Armstrong R , et al. Comparing contents of outcome measures in cerebral palsy usingthe International Classification of Functioning (ICF-CY): a systematic review. Eur J Paediatr Neurol 2013;18:1-12.
14. Hsieh YL, Yang CC, Sun SH, Chan SY, Wang TH, Luo HJ. Effects of hippotherapy on body functions, activities and participation in children with cerebral palsy based on ICF-CY assessments. Disabil Rehabil 2016;20:1-11.
15. Russell DJ, Avery LM, Rosenbaum PL, Raina PS, Walter SD, Palisano RJ. Improvedscaling of thegross motor function measure for children with cerebral palsy: evidence of reliability and validity. Phys Ther 2000;80:873-85.
16. Erkin G, Aybay C. Pediatrik Rehabilitasyonda Kullanılan Fonksiyonel Derğerlendirme Metodları. Türkiye Fiziksel TİP Ve Rehabilitasyon Değerlendirme 2001;47;16-26.
17. Franjoine MR, Gunther JS, Taylor MS. Pediatric Balance Scale: a modified version of the Berg Balance Scale for the school-age child with mild to moderate motor impairment. Pediatr Phys Ther 2003;15:114-20.
18. Özel C, Günel MK. Investigation of the relationship between trunk control, functional mobility, and balance in children with spastic cerebral palsy. J Exerc Ther Rehabil 2014;1:1-8.
19. McDowell B, Humphreys L. Test–retest reliability of a 1-min walk test in children with bilateral spastic cerebral palsy (BSCP). Gait Postur 2009;29:267-9.
20. Tekin F, Kavlak E, Cavlak U, Altug F. Effectiveness of Neuro-Developmental Treatment (Bobath Concept) on postural control and balance in Cerebral Palsied children. J Back Musculoskelet Rehabil 2018;31:397-403.
21. Aybay C, Erkin G, Elhan AH, Sirzai H, Ozel S. ADL assessment of non disabled Turkish children with the PFBÖ instrument. AM J Phys Med Rebabil 2007;86:176-82.
22. Waters E, Wright M, Wake M, Landgraf JM, Salmon L. Measuring the health and well being of children and adolescents: A preliminary comparative evaluation of the Child Health Questionnaire (CHQ-PF50). Ambulatory Child Health 1999;5:131-41.
23. Sümbüloğlu,V. Sümbüloğlu K. Sağlık Bilimlerinde Araştırma Yöntemleri, Hatipoğlu Yayıncılık, Ankara. 2005.
24. Okochi J, Utsunomiya S, Takahaski T. Health measurement using the ICF: Test-retest reliability study of ICF codes and qualifiers geriatric care. Health Qual Life Outcomes 2005;3:46.
25. Kabakçı E, Göğuş A. T.C. BÖİB. İşlevsellik, Yetiyitimi ve Salığın Uluslararası Sınıflandırması. Bilge Matbaacılık. Ankara. 2001.
26. Benner JL, Noten S, Limsakul C, Van Der Slot WMA, Stam HJ, Selb M, et al. Outcomes in adults with cerebral palsy: systematic review using the International Classification of Functioning, Disability and Health. Dev Med Child Neurol 2019;61:1153-61.
27. Pihlar Z. From activity to participation occupational therapy intervention for CP children. Eastern J of Med 2012;17:198-201.
28. Hurley DS, Sukal-Moulton T, Gaebler-Spira D, Krosschell KJ, Pavone L, Mutlu A, et al. Systematic review of cerebral palsy registries/ surveillance groups: Relationships between registry characteristics and knowledge dissemination. Int J Phys Med Rehabil 2015;3:266.
29. Engelen V, Ketelaar M, Gorter JM. Selecting the appropriate outcome in paediatric physical therapy: How individual treatment goals for children with cerebral palsy are reflected in KMFÖ-88-88 and PEDI. J Rehabil Med 2007;39:225-31.
30. Jeglinsky I, Carlberg EB, Autti-Rämö I. How are actual needs recognized in the content and goals of written rehabilitation plans? Disabil Rehabil 2014;36:441-51.

31. Ogonowski J, Kronk R, Rice C, Feldman H. Inter-rater reliability in assigning ICF codes to children with disabilities. Disabil Rehabil 2004;26:353-61.

32. Livanelioğlu A, Kerem M. Serebral Palside Fizyoterapi, Yeni Özbek Matbaası, Ankara, 2009.

33. Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. Cerebral palsy in Norway: prevalence, subtypes and severity. Eur J Paediatr Neurol 2008;12:4-13.

34. Dilşen G. Sakatlık ve Rehabilitasyon Süreci, In:Beyazova M., Gökçe-Kutsal Y. eds. Fiziksel Tıp ve Rehabilitasyon: Güneş Kitabevi, Ankara, 2000;18-36s.

35. Tomás CC, Oliveira E, Sousa D, Uba-Chupel M, Furtado G, Rocha C, et al. Application of the International Classification of Functioning, Disability and Health (Children and Youth Version) in the Evaluation of Rehabilitation Measures of Patients with Cerebral Palsy. BMC Health Serv Res 2020;5:38-45.

36. Mutlu A, Akmese PP, Gunel Mk, Karahan S, Livanelioglu A. The importance of motor Functional levels from the activity limitaion perspective of ICF in children with cerebral palsy. Int J Rehabil Res 2010;4:319-24.

Original Article

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Comparative Analysis of Tertiary Stroke Center: Factors Affecting the 3rd Month Clinical Outcome of Patients Treated with Thrombolytic Treatment

Üçüncü Basamak İnme Merkezinin Iv-tPA Deneyimi: Trombolitik Tedavi Uygulanan Hastalarda 3. Ay Klinik Sonlanıma Etki Eden Faktörler

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ABSTRACT

Objective: In this study, we aimed to document the data of intravenous thrombolytic therapy [intra venous tissue plasminogen activator (iv-tPA)] that we applied to patients admitted to our stroke unit with acute ischemic stroke, and to verify the correlation of these data with the 3rd month modified Rankin Scale (mRS) score.

Methods: We enrolled 235 patients in the study who were admitted to İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital with acute ischemic stroke and received iv-tPA. Demographic data of the patients and stroke risk factors were recorded. Trial of Org 10172 in acute stroke (TOAST) classification for stroke etiology, Bamford stroke classification to define stroke clinic, "National Institute of Health Stroke Scale" score to evaluate stroke severity, and "the Alberta stroke program early CT" (ASPECT) score to evaluate the brain tomography of patients before iv-tPA were used. The 3rd month functional outcomes were evaluated with the mRS score. The correlation between all data obtained from the patients and mRS score was examined.

Results: Two hundred thirty five patients who received iv-tPA (128 females, 107 males, mean age 72.23±13.88) were included in the study. It was observed that patients with atrial fibrillation rhythm and patients who developed complications during hospitalization had significantly higher mRS scores. When the relationship between TOAST classification subgroups and mRS score was examined, it

ÖZ

Amaç: Bu çalışmada inme ünitemize akut iskemik inmeyle başvuran hastalara uyguladığımız intravenöz trombolitik tedavi [intravenous tissue plasminogen activator, (iv-tPA)] verilerini dokümante etmeyi ve bu verilerin 3. ay modifiye Rankin Skalası (mRS) skoru ile korelasyonunu incelemeyi amaçladık.

Yöntemler: İstanbul Medeniyet Üniversitesi Göztepe Prof. Dr. Süleyman Yalçın Şehir Hastanesi İnme Ünitesi'ne akut iskemik inme ile başvuran ve iv-tPA uygulanan 235 hasta çalışmaya alındı. Hastaların demografik verileri ve inme risk faktörleri kaydedilmiştir. İnme etiyolojisi için Trial of Org 10172 in acute stroke (TOAST) sınıflaması, inme kliniğini tanımlamak için Bamford inme sınıflaması, inme şiddetini değerlendirmek amacıyla "National Institute of Health Stroke Scale", iv-tPA öncesi hastaların beyin tomografisini değerlendirmek için "The Alberta stroke programme early CT score" (ASPECT) skoru kullanılmıştır. Hastaların 3. ay sonundaki fonksiyonel sonlanımları mRS skoru ile değerlendirilmiştir. Hastaların elde edilen tüm verileri ile mRS skoru arasındaki korelasyon bakılmıştır.

Bulgular: Çalışmaya iv-tPA tedavisi alan 235 hasta (128 kadın, 107 erkek, yaş ortalaması 72,23±13,88) dahil edilmiştir. Yatış komplikasyonu gelişen ve atrial fibrilasyon ritmi olan hastaların mRS skorlarının anlamlı şekilde daha yüksek olduğu görüldü. TOAST sınıflaması alt gruplarıyla mRS arasındaki ilişkiye bakıldığında,

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was found that the large artery atherosclerosis and cardioembolism groups had higher mRS score than the small vessel disease and undetermined etiology groups. According to the Bamford classification, the total anterior circulation syndrome group had a higher mRS score than all other groups. A negative correlation was detected between ASPECT score and mRS score.

Conclusion: As a result of this study, Bamford and TOAST classifications, ASPECT score, the presence of atrial fibrillation rhythm, and the development of complications during hospitalization were important factors in predicting 3rd month disability of the patients who were treated with iv-tPA.

Keywords: Thrombolytic therapy, modified rankin scale, disability, stroke

büyük arter aterosklerozu ve kardiyoembolizm gruplarının, küçük damar hastalığı ve etiyolojisi belirlenemeyen gruplara göre daha yüksek mRS 3 değerlerine sahip olduğu bulundu. Bamford sınıflamasına göre Tacs grubu diğer tüm gruplardan daha yüksek mRS skoruna sahipti. ASPECT skoru ve mRS skoru arasında negatif korelasyon tespit edildi.

Sonuç: Bu çalışmada elde edilen verilere göre trombolitik tedavi verilen hastaların Bamford ve TOAST sınıflamalarının, ASPECT skorunun, atrial fibrilasyon ritminin varlığının ve yatış komplikasyonunun gelişmesinin hastaların 3. aydaki engelliliğini tahmin etmede önemli faktörler olduğu sonucuna varılmıştır.

Anahtar Sözcükler: Trombolitik tedavi, modifiye rankin skalası, engellilik, inme

Introduction

Ischemic stroke, known as incurable for a long time, has reached an exciting point thanks to proven treatments that have taken their place in neurology practice in the last decades (1). Intravenous tissue plasminogen activator (iv-tPA) and mechanical thrombectomy have taken their place in clinical practice as treatment options that have proven to have a great effect on mortality and morbidity of stroke. With these treatment methods, it is aimed to provide recanalization and reperfusion in brain tissue with impaired oxygenation and protect the penumbra. Thus, it is aimed to restore the brain functions lost due to stroke and to prevent additional neural damage that may occur in the following hours. Recently, the prevalences of the main risk factors for ischemic stroke such as sedentary lifestyle habits, obesity which was becoming a global public health problem, and drug and tobacco use have increased. Thus, the importance of acute stroke management and treatment practices is increasing (2). Despite the increase in the prevalence of stroke, ischemic stroke has regressed from the 3rd most common cause of death worldwide to the 5th place in recent years, thanks to the acute interventions that have been developed (3). The biggest obstacle to treatments is the inability of patients to reach stroke centers where they can receive appropriate treatment during the acute intervention period. Today, the majority of stroke patients cannot receive acute treatment because they are not admitted to the hospital in the appropriate time (4). The time window of treatment, which was determined as the first three hours for intravenous thrombolytic therapy, was extended to the first 4.5 hours with the stroke guideline updated in 2013, and the number of studies supporting that this treatment can be given up to 9 hours in selected patients are increasing (5-7). In the stroke guidelines, the importance of pre-hospital organization, establishing in-hospital stroke teams, and evaluation of patients with tele-medicine before they come to the hospital are emphasized in order to give appropriate treatment to the patients during these periods (6).

In this study, we documented the data of iv-tPA treatment that we gave to patients who were admitted with acute ischemic stroke since the stroke unit was established in our hospital (2018-2021) and the correlation of these data with the 3rd month modified Rankin Scale (mRS) score, by categorizing the patients according to the time intervals of treatment (0-3 hours, 3-4.5 hours and >4.5 hours).

Methods

For this study, the Ethics Committee approval was obtained from İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee with the decision number 2021/0187 and date 10.03.2021. We enrolled 235 patients in the study who were admitted to İstanbul Medeniyet University Göztepe Training and Research Hospital Stroke Unit with acute ischemic stroke and received iv-tPA between January 2018 and May 2021. The medical records of the patients were reviewed retrospectively, and demographic (age, gender) and clinical data (vascular risk factors, symptom-door, door-needle times, undergoing thrombectomy after iv-tPA, complications due to iv-tPA, complications during hospitalization) were obtained. Cranial tomography and craniocervical CT angiography were performed in all patients as the protocol of the stroke center before iv-tPA. At the 24th hour after iv-tPA, control imaging was obtained with tomography or cranial magnetic resonance imaging with gradient echo sequence. Patients were categorized into three groups according to treatment time intervals (0-3 hours, 3-4.5 hours and >4.5 hours). Iv-tPA was given after 4.5 hours only to the patients in the wake-up stroke category in which the onset of symptoms was unclear, and when diffusion FLAIR mismatch was detected.

The TOAST (Trial of Org 10172 in acute stroke) classification for stroke etiology, Bamford stroke classification to define stroke clinic, "National Institute of Health Stroke Scale" (NIHSS) score (acute period - discharge - 1st month) to evaluate stroke severity, "the Alberta stroke program early CT" (ASPECT) score to evaluate the brain tomography of patients before iv-tPA were used. The functional outcomes of the patients at the end of the 3rd month were evaluated with the mRS score. Patients with mRS 0-2 were determined as having good outcome, and patients with mRS 3-6 were determined as having poor outcome. All the data obtained were subjected to comparative analysis with the mRS score.

Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used. The distribution of the data were evaluated with the Shapiro-Wilk Test. Kruskall-Wallis test was used for comparison of quantitative data of three or more groups; Mann-Whitney U Test was used for comparison of two groups. Linear regression analysis was used to determine the factors affecting the dependent variable. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

Results

Two hundred thirty five patients who received iv-tPA (128 females, 107 males, mean age 72.23±13.88) were included in the study. The stroke risk factors and etiological classification data of the patients are given in Table 1. Admission NIHSS scores did not show statistically significant difference according to iv-tPA delivery time ($p>0.05$). It was found statistically significant that the admission NIHSS score of the thrombectomy group was higher than the group that did not undergo thrombectomy ($p=0.001$ and $p<0.01$) (Table 2).

Table 3 contains data on the relationship between stroke risk factors and mRS score. It was found statistically significant that the 3rd month mRS score of the patients who developed complication during hospitalization was higher than the group without complication ($p=0.001$ and $p<0.01$). The 3rd month mRS score of the group with AF was found to be statistically significantly higher than the group without AF ($p=0.001$ and $p<0.01$) (Table 3). The mRS scoreat the 3rd month showed a statistically significant difference between iv-tPA application times ($p=0.044$ and $p<0.05$). The 3rd month mRS score of the group that received iv-tPA within 0-3 hours was statistically significantly higher than that of the group that received iv-tPA within 3-4.5 hours ($p=0.001$ and $p<0.05$). Considering the relationship between TOAST classification subgroups and mRS score, large artery atherosclerosis (LAA) group and cardioembolism group were found to have higher mRS score than small vessel disease and undetermined etiology groups ($p=0.001$ and $p<0.05$). In the Bamford classification, TACS group had a higher mRS score than all other groups ($p=0.001$ and $p<0.05$). It was observed that the 3rd month mRS scores of the thrombectomy group were significantly higher than the group that did not undergo thrombectomy ($p=0.001$ and $p<0.01$) (Table 4).

In Table 5, the multiple linear regression analysis was performed to determine the effect of independent variables on the 3rd month mRS score ($F=18.628$, $p<0.001$). There was a positive and highly significant relationship between independent variables and 3rd month mRS score ($R=0.725$, $p<0.01$). The independent

Table 1. The stroke risk factors and etiological classification data of the patients

		n	%
Sex	Female	128	54.5
	Male	107	45.5
Hypertension	No	55	23.4
	Yes	180	76.6
Hyperlipidemia	No	131	55.7
	Yes	104	44.3
Diabetes mellitus	No	151	64.3
	Yes	84	35.7
Atrial fibrillation	No	142	69.8
	Yes	93	30.2
Smoking	No	164	69.8
	Yes	71	30.2
iv-tPA	0-3 hours	159	67.7
	3-4.5 hours	65	27.7
	>4.5 hours	11	4.7
TOAST classification	Large artery atherosclerosis	34	14.9
	Small vessel oclusion	39	17.1
	Cardioembolism	118	51.8
	Undetermined etiology	37	16.2
Bamford classification	Tacs	9	3.9
	Pacs	154	67.2
	Pocs	41	17.9
	Lacs	23	10.0
	Mixed	2	0.9

iv-tPA: Intravenous tissue plasminogen activator, TOAST: Trial of Org 10172 in acute stroke

variable in the model explains 52.5% of the total variance of the 3rd month mRS score (p<0.01). When the regression coefficients were examined, the ASPECT score (β=-0.122, p<0.01) had a negative effect on the 3rd month mRS score; age (β=0.18, p<0.01), complications during hospitalization (β=0.49, p<0.01) and thrombectomy (β=0.153, p<0.01) had a positive and significant effect on the 3rd month mRS score (Table 5).

Discussion

In this study, we aimed to analyze the data of patients who received iv-tPA treatment within 3 years in our stroke center and to observe the effect of these data on the 3rd month disability score. The presence of AF and complications due to hospitalization had a negative effect on the 3rd month mRS score. It was observed that the 3rd month mRS scores of the small vessel disease group in the TOAST classification and the lacunar syndrome (Lacs) group in the Bamford classification were significantly lower than the other groups. The 3rd month mRS score was found to be significantly higher in the patients who underwent thrombectomy. This was attributed to the significantly higher NIHSS scores at admission in this patient group due to LAA.

Patients who received iv-tPA between 3-4.5 hours had lower mRS scores at 3 months compared to the group that received iv-tPA in the first three hours. Although this result contradicts the knowledge that the sooner patients receive iv-tPA treatment, fewer neurons will die and the pneumbra will be more protected, we see that patients who receive treatment within the first 3 hours have higher admission NIHSS scores.

In the lineer regression analysis data, a significant direct correlation was found between age and 3rd month mRS score. As the age progresses, the effectiveness of treatment is lower and the disability in the 3rd month is higher. As expected, the ASPECT score was inversely correlated, and patients with higher ASPECT scores had lower mRS 3 scores because they started treatment with more preserved brain tissue. Complications due to

Table 2. Patients' admission NIHSS scores

		NHISS scores		
		Mean ± SD+	Min-max (median)	P
iv-tPA time	0-3 hours	9.62±5.66	2-24 (8)	0.191[a]
	3-4.5 hours	8.58±5.74	2-22 (6)	
	>4.5 hours	7.27±3.35	3-15 (7)	
Thrombectomy	No	8.05±5.01	2-24 (7)	0.001**[b]
	Yes	13.87±5.5	4-23 (15)	

[a]Kruskall-Wallis Test, [b]Mann-Whitney U Test, NIHSS: National Institute of Health Stroke Scale, iv-tPA: Intra venous tissue plasminogen activator, *p<0.05, **p<0.01, Mean ± SD+: Mean ± standard deviation

Table 3. Relationship of stroke risk factors with 3rd month mRS score

		3rd Month mRS score		
		Mean ± SD+	Min-max (median)	P
Sex	Female	1.94±2.22	0-6 (1)	0.926
	Male	1.89±2.09	0-6 (1)	
Complication during hospitalization	No	1.11±1.56	0-6 (0)	0.001**
	Yes	4.13±2	0-6 (5)	
Hypertension	No	1.58±2.04	0-6 (0)	0.144
	Yes	2.02±2.19	0-6 (1)	
Hyperlipidemia	No	2.07±2.29	0-6 (1)	0.453
	Yes	1.72±1.96	0-6 (1)	
Diabetes mellitus	No	1.98±2.18	0-6 (1)	0.618
	Yes	1.8±2.12	0-6 (1)	
Atrial fibrillation	No	1.45±1.83	0-6 (1)	0.001**
	Yes	2.61±2.43	0-6 (2)	
Coronary artery disease	No	1.71±2.03	0-6 (1)	0.084
	Yes	2.32±2.36	0-6 (2)	
Smoking	No	2.05±2.2	0-6 (1)	0.070
	Yes	1.59±2.02	0-6 (0)	
Drug addiction	No	1.92±2.16	0-6 (1)	0.290
	Yes	0±0	0-0 (0)	

Mann-Whitney U *p<0.05, **p<0.01, Mean ± SD+: Mean ± standard deviation

Table 4. Relationship of stroke data with 3rd month mRS score

		3rd Month mRS score		
		Mean ± SD+	Min-max (median)	P
t-PA administration	0-3 hours	2.07±2.21	0-6 (1)	0.044**a
	3-4.5 hours	1.39±1.87	0-6 (0)	
	>4.5 hours	2.73±2.53	0-6 (2)	
TOAST classification	Large artery atherosclerosis	2.39±2	0-6 (3)	0.001**a
	Small vessel oclusion	0.64±1.06	0-4 (0)	
	Cardioembolism	2.48±2.34	0-6 (2)	
	Undetermined etiology	1.11±1.76	0-6 (0)	
Bamford classification	Tacs*	5.11±1.17	3-6 (6)	0.001**a
	Pacs*	2.27±2.22	0-6 (2)	
	Pocs*	0.78±1.24	0-6 (0)	
	Lacs*	0.74±1.21	0-4 (0)	
	Miks	0±0	0-0 (0)	
Use of antiplatelet/ anticoagulant	No	1.82±2.22	0-6 (1)	0.741a
	Antiplatalet	2.02±2.05	0-6 (1.5)	
	Anticoagulant	2±2.27	0-6 (1)	
	Both	2.5±3.54	0-5 (2.5)	
Complication due to iv-tPA	No	1.86±2.14	0-6 (1)	0.136b
	Yes	2.59±2.29	0-6 (2)	
Thrombectomy	No	1.57±1.93	0-6 (1)	0.001**b
	Yes	3.33±2.47	0-6 (3.5)	

aKruskall-Wallis Test, bMann-Whitney U Test, *p<0.05 **p<0.01, +Tacs: Total anterior circulation syndrome, Pacs: Partial anterior circulation syndrome, Pocs: Posterior circulation syndrome, Lacs: Lacunar syndrome. Mean ± SD+: Mean ± standard deviation

Table 5. Linear regression analysis findings for the relationship between independent variables and 3rd month mRS score

		Univariable					Multivariable				
Model	Variables	B	SD+	Standard (B)	t	p	B	SD	Standard (B)	t	p
1	Age	0.052	0.010	0.335	5.411	0.001**	0.028	0.008	0.18	3.4	0.001**
	ASPECT score	-0.655	0.154	-0.269	-4.262	0.001**	-0.296	0.12	-0.122	-2.466	0.001**
	Hospitalization Complication-Yes	3.021	0.25	0.623	12.108	0.001**	2.375	0.25	0.49	9.491	0.001**
	AF-Yes	1.159	0.279	0.263	4.160	0.001**					
	Thrombectomy	1.757	0.336	0.324	5.223	0.001**	0.833	0.282	0.153	2.95	0.001**
	iv-tPA-3-4.5 hours	-0.721	0.313	-0.149	-2.300	0.001**					
	Toast-small vessel occlusion	-1.528	0.366	-0.265	-4.179	0.001**					
	Toast-cardioembolism	1.147	0.272	0.266	4.209	0.001**					
	Toast-Undetermined	-0.958	0.382	-0.162	-2.506	0.001**					
	Bamford-TACS	-0.802	0.162	-0.310	-4.966	0.001**					
	Bamford-PACS	1.021	0.289	0.226	3.528	0.001**					
	Bamford-POCS	-1.375	0.361	-0.243	-3.813	0.001**					
	Bamford-LACS	-1.304	0.467	-0.180	-2.792	0.001**					

*p<0.05, **p<0.01, +SD: Standard deviation

hospitalization in stroke patients are a major factor on mortality and morbidity. As a result of this study, it was concluded that the 3rd month disability of the patients with complications due to hospitalization was higher.

The mRS constitutes one of the most reliable scales used globally to score the third month endpoint outcome in stroke patients (8). It also shows the success of acute stroke treatments by showing the disability and dependence of the patients in the third month after the stroke (9). In a meta-analysis by Li et al., (10) the effect of early mobilization on acute stroke patients was examined with mRS score, and it was shown that the shorter hospital stay was associated with better outcomes. Similarly, in this study, complication due to hospitalization was shown to be associated with worse mRS scores.

The most avoided complication of acute thrombolytic therapy is bleeding. Intracerebral hemorrhage, which develops as a treatment complication, is associated with high mortality (10). Complications of symptomatic intracranial hemorrhage were reported at a rate of 2.4% in the European Cooperative Acute Stroke Study 3 (ECASS 3) and 7% in the "Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke Study" (11,12). Similar to the literature, bleeding complications were observed after iv-tPA in 7.23% of the patients. As a result of this study, no significant difference was observed between the patient groups who developed and did not develop iv-tPA bleeding complications in terms of 3rd month mRS scores.

As a result of the stroke project conducted by Antonio Di Carlo et al. (13), it was observed that the risk of death at the 3rd month significantly increased in total anterior circulation infarctions (TACI) group patients compared to lacunar infarctions group patients. In the same study, it was shown that atrial fibrillation was predictive for TACI (13). In this study, it was observed that the mRS score of the patients in the LAA and TACS (total anterior circulation syndrome) groups were significantly lower. The presence of atrial fibrillation also had a significant negative effect on mRS score.

In the ECASS-4 study, iv-tPA treatment was given to acute stroke patients between 4.5 and 9 hours who met the criteria of infarct core volume <100 mL, perfusion lesion: infarct core mismatch ratio >1.2 and perfusion lesion minimum volume of 20 mL. As a result of the study, it was reported that the time of administration of thrombolytic therapy could be extended in selected patients (7). No treatment complications were observed in 11 patients included in this study who were given iv-tPA >4.5 hours and they benefited from the treatment. There was no significant difference between the 3rd month mRS scores of the three groups. This result led us to the conclusion that thrombolytic therapy should be given to selected patients in support of ECASS-4 (7).

Study Limitations

For more efficient statistical analysis, the number of patients given iv-tPA >4.5 hours should be higher. Likewise, the retrospective design of the study creates a limitation in terms of accessing patient data.

Conclusion

Iv-tPA is a safe and effective treatment for acute stroke. Clinical stroke classifications and defining stroke risk factors during acute stroke are useful in estimating the 3rd month mRS score.

Ethics

Ethics Committee Approval: For this study, the Ethics Committee approval was obtained from İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee with the decision number 2021/0187 and date 10.03.2021.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.H.K., R.Ş., D.Ç., S.Ö., Z.T.Y., O.İ., K.A., Concept: H.H.K., R.Ş., O.İ., K.A., Design: R.Ş., D.Ç., Data Collection or Processing: R.Ş., D.Ç., S.Ö., Analysis or Interpretation: H.H.K., O.İ., K.A., Literature Search: R.Ş., Writing: R.Ş.

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References

1. Rabinstein AA. Update on Treatment of Acute Ischemic Stroke. Continuum (Minneap Minn) 2020;26:268-86.
2. George MG. Risk Factors for Ischemic Stroke in Younger Adults: A Focused Update. Stroke 2020;51:729-35.
3. Prabhakaran S, Ruff I, Bernstein RA. Acute Stroke Intervention: A Systematic Review. JAMA 2015;313:1451-62.
4. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke 2009;40:2945-8.
5. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947.

6. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418. Epub 2019 Oct 30. Erratum in: Stroke 2019;50:e440-e1.
7. Amiri H, Bluhmki E, Bendszus M, Eschenfelder CC, Donnan GA, Leys D, Molina C, Ringleb PA, Schellinger PD, Schwab S, Toni D, Wahlgren N, Hacke W. European Cooperative Acute Stroke Study-4: Extending the time for thrombolysis in emergency neurological deficits ECASS-4: ExTEND. Int J Stroke 2016;11:260-7.
8. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke 2017;48:2007-12.
9. Cappellari M, Moretto G, Bovi P. Day-7 modified Rankin Scale score as the best measure of the thrombolysis direct effect on stroke? J Thromb Thrombolysis 2013;36:314-5.
10. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-7.
11. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-29.
12. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA 1999;282:2019-26.
13. Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Consoli D, Wolfe CD, Giroud M, Rudd A, Burger I, Ghetti A, Inzitari D; European BIOMED Study of Stroke Care Group. Risk factors and outcome of subtypes of ischemic stroke. Data from a multicenter multinational hospital-based registry. The European Community Stroke Project. J Neurol Sci 2006;244:143-50.

Original Article

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Evaluation of the Relationship Between Maxillary Labial Frenulum Attachment Types, Periodontal Health, and Dental Caries in Preschool Children

Okul Öncesi Çocuklarda Maksiller Labial Frenulum Ataçman Tipleri ile Periodontal Sağlık ve Diş Çürükleri Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: The purpose of the study was to investigate any possible relation between maxillary labial frenulum attachment type on periodontal status and dental caries in pre14school children.

Methods: This cross-sectional study was conducted for six months among the children who were admitted for treatment at a university clinic. The children aged between 3 to 6 years were enrolled in the study. The types of maxillary labial frenulum attachment were recorded as mucosal, gingival, papillary, and papillary penetrating types. Plaque index (PI), gingival index (GI), and dental status (dmft) of maxillary primary incisors were evaluated. Kruskal-Wallis and Pearson's chi-squared tests were used for statistical analysis.

Results: A total of 214 children (mean age was 4.4±0.9 years) were evaluated. The most common maxillary frenulum attachment type was the gingival type (45.8%), while the papillary penetrating type (13.1%) was the least common. The PI and GI scores in children with mucosal type frenulum were lower than in children with the gingival, papillary, and papillary penetrating types ($p<0.01$). The dmft scores were lower in children with mucosal type frenulum and higher in children with papillary type frenulum ($p<0.01$).

Conclusion: Papillary and papillary penetrating types of frenulum attachments were associated with a decline in periodontal health and higher caries incidence in maxillary primary incisors.

Keywords: Oral health, caries, maxillary frenulum, periodontal health

ÖZ

Amaç: Bu çalışmanın amacı, okul öncesi çocuklarda maksiller labial frenulum ataçman tipi ile periodontal sağlık ve diş çürükleri arasında olası bir ilişki olup olmadığını araştırmaktır.

Yöntemler: Kesitsel tipteki bu araştırma, bir üniversite kliniğine tedavi için başvuran çocuklarda 6 aylık bir süre boyunca yürütülmüştür. Çalışmaya 3 ila 6 yaş arasındaki çocuklar dahil edilmiştir. Maksiller labial frenulum ataçmanının tipi mukozal, gingival, papiller ve papillaya penetre olarak kaydedilmiştir. Maksiller süt kesici dişlerin plak indeksi (Pİ), gingival indeksi (Gİ) ve çürük durumu (dmft) değerlendirilmiştir. İstatistiksel analiz için Kruskal-Wallis ve Pearson ki-kare testleri kullanılmıştır.

Bulgular: Toplam 214 çocuk (ortalama yaş: 4,4±0,9) değerlendirilmiştir. En sık görülen maksiller frenulum ataçman tipi gingival tip (%45,8) iken, en az görülen ise papillaya penetre tip (%13,1) olmuştur. Mukozal tip frenuluma sahip çocuklarda Pİ ve Gİ skorları gingival, papiller ve papillaya penetre tipteki çocuklara göre daha düşüktür ($p<0,01$). Mukozal tip frenuluma sahip çocuklarda dmft skorları daha düşük iken, papiller tip frenulumlu çocuklarda ise daha yüksektir ($p<0.01$).

Sonuç: Papiller ve papillaya penetre tip frenulum ataçmanları, periodontal sağlığı olumsuz etkilemiş ve maksiller süt kesici dişlerde daha yüksek çürük insidansı görülmesine neden olmuştur.

Anahtar Sözcükler: Ağız sağlığı, diş çürüğü, maksiller frenulum, periodontal sağlık

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Introduction

The frenulum, one of the most interesting anatomic structures in the oral cavity, is a collagenous fibrous tissue fold of mucous membrane and connects the lip, cheeks, and tongue to the alveolar process. It originates embryologically from a residue of cells of the vestibular lamina at the midsagittal area, consisting mostly of connective tissue and epithelium, which rarely contain muscle fibers (1,2). There are seven types of frenulum described in the literature; most prominently the maxillary labial frenulum, the mandibular labial frenulum, the lingual frenulum, and four buccal frenula, generally present in the oral cavity (3). Although their primary function is providing stability in the maxilla and mandible, there is controversy about their contribution to mastication (4).

The notable maxillary labial frenulum has been associated with several clinical problems in infants or children. The most prominent complication is midline diastema, occurring as a result of preventing contact between maxillary incisors, whereas it is a physiologic condition during the early developmental stage (5). The midline diastema is a major esthetic problem for children and parents; it may also complicate orthodontic treatment and can be possibly responsible for the progression of dental caries in breastfeeding children. Breastfeeding or bottle-feeding difficulties occurring as a result of inhibition of sealing on the maternal breast or feeding bottle could be associated with a restrictive maxillary labial frenulum in newborns (6). As also a local anatomic factor, the maxillary labial frenulum may cause dental plaque accumulation. The limited toothbrushing ability of children can be affected and removing the plaque can be more difficult (5).

The free or gingival insertion level of hyperplastic maxillary frenulum attachment may complicate cleaning the maxillary incisors by preventing the movement of the upper lip. It potentially leads to dental caries, especially in facial-cervical regions (7). Dental caries is a common disease that affects most of the populations around the world. In children, early childhood caries (ECC) is defined as the presence of one or more decayed, missing (due to caries), or filled tooth surfaces in any primary tooth in a child younger than 6 years. One of the main etiologic factors of ECC is inadequate oral hygiene. The removal of plaque on the teeth surfaces is predisposing to the formation of dental caries. Facial-cervical caries lesions are frequently observed in the maxillary anterior region in children (8).

The clinical morphological classification of the maxillary labial frenulum was described by Placek et al. (9). The classification depends on the anatomical insertion level of attachment and aims to help clinicians for identifying functional problems. The maxillary labial frenulum İs classified according to whether the attachment İs located at the mucogingival junction, the attached gingiva, the interdental papilla, and through the interdental papilla to the palate (7). The position of insertion, shape, or structure of the maxillary labial frenulum can change during the growth and development period due to its dynamic nature (10). Although the prevalence of different types of maxillary labial frenulum has been studied in adults, there are only a few studies investigating this classification in children (5,11).

Although anecdotal theories sustain, there is no evidence supporting these clinical results to date. Considering this limited information, the purpose of this cross-sectional study was to investigate any possible relation between maxillary labial frenulum attachment type on periodontal problems and dental caries in children. In addition, the prevalence of maxillary labial frenulum attachment type was described in a Turkish population.

Methods

Statement of Ethics

Ethical approval was obtained from the Research Ethics Committee of Bezmialem Vakıf University in full accordance with the ethical principles of the Helsinki Declaration (protocol no. 04.11.2020- 12/24). Written informed consent from the parents and verbal assent from the children were also obtained.

Study Design and Participants

This cross-sectional study was performed at the Bezmialem Vakıf University Pediatric Dentistry Clinic between November 2020 and May 2021. The physically healthy children aged between 3 to 6 years were enrolled in the study. Children who were admitted to the clinic for a routine dental examination, fulfilled inclusion criteria, and were willing to participate were included in the study. The children with congenital or developmental anomalies, history of trauma or surgical operation on the maxillary anterior region, and under any medication affecting the gingiva were excluded from the study. Demographical data such as age and gender were recorded.

Clinical Examination

The clinical examinations were performed in the dental unit under adequate lighting with experienced two pediatric dentists. Children were examined to record the type of maxillary frenulum. In addition, oral hygiene of children and dmft, plaque index (PI), and gingival index (GI) score of maxillary primary incisors were assessed. An adjusted scoring chart was used when scoring the clinical outcomes (Table 1).

The maxillary labial frenulum attachment was categorized as mucosal, gingival, papillary, and papilla penetrating according to the classification of Placek et al. (9). If the frenal fibers are attached up to the mucogingival junction, it is classified as mucosal; if the frenal fibers are inserted within the attached gingiva, it is classified as gingival; if the frenal fibers are extending into the interdental papilla, it is classified as papillary and if the frenal fibers cross the alveolar process and extend up to the palatine papilla, it is classified as papilla penetrating (Figure 1).

Periodontal health was assessed using the PI and GI. The means of four surfaces (mesial, distal, buccal, lingual) were used as the PI and GI scores. Microbial dental plaque accumulation of the maxillary incisors was assessed with the PI, according to Silness and Loe (12). Gingival health was assessed using the GI, according to Loe and Silness (13).

Dental status was reported using the World Health Organization criteria for deciduous teeth (14). The dmft index of maxillary

primary incisors was recorded by examiners using a dental mirror and explorer under dental unit lighting. To determine the dmft index, summation of decayed, missed, and filled maxillary primary incisors was calculated. The dmft scores were categorized as <1 and ≥1 to analyze the data.

Statistical Analysis

Statistical analyses were performed using SPSS software for Windows (Ver. 12.0, IBM Corp., Chicago, Ill., USA) at a significance level of α=0.05. Intra- and interobserver reliability were assessed with the intraclass correlation coefficient. Descriptive statistics were presented as the mean ± standard deviation. All data were tested for normal distribution with the Shapiro-Wilk test. Pearson's chi-square and Kruskal-Wallis tests with Bonferroni correction were used for comparisons.

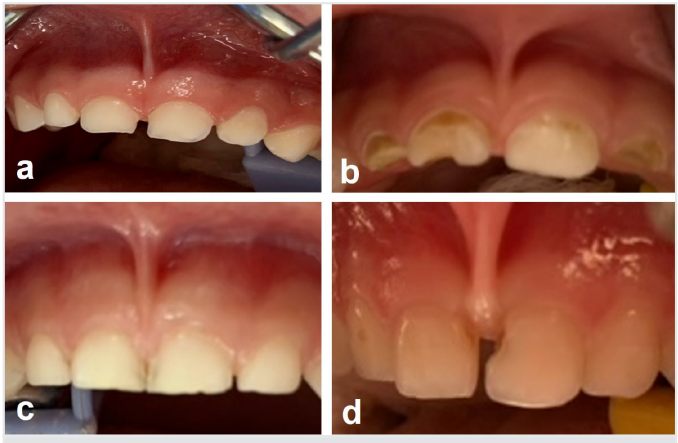

Figure 1. Examples of maxillary labial frenulum attachment types. **(a)** Mucosal, **(b)** gingival, **(c)** papillary, **(d)** papillary penetrating

Table 1. Clinical assessment criteria

Type of maxillary frenulum attachment[9]	0: mucosal 1: gingival 2: papillary 3: papilla penetrating
dmft	0: <1 1: ≥1
Plaque index[12]	0: no plaque 1: film at the gingival margin and adjacent tooth 2: moderate accumulation 3: abundance on a plaque
Gingival index[13]	0: normal gingiva 1: mild inflammation 2: moderate inflammation 3: severe inflammation

Results

A total of 214 children were included in the present study. The children included 96 boys and 118 girls whose ages ranged from 3 to 6 years (mean age was 4.4± 0.9 years). The intra- and interobserver kappa values were above 0.8 and 0.6 for the PI and GI measurements, respectively.

The prevalence of maxillary frenulum attachments is shown in Figure 2. The most common attachment type was the gingival type (45.8%), whereas papillary type (23.8%) and mucosal type (17.3%) attachments were less common, and the least common attachment type was the papillary penetrating type (13.1%).

The PI and GI scores of maxillary primary incisors were significantly different among the maxillary frenulum attachment types (Table 2). Post-hoc analysis revealed that the PI and GI scores of maxillary primary incisors in children with mucosal type frenulum were lower than in children with gingival type, papillary type, and papillary penetrating type frenulum ($p< 0.01$). The PI and GI scores of maxillary primary incisors in children with gingival type frenulum were lower than in children with papillary type and papillary penetrating type frenulum ($p<0.01$).

The dental status of the children, as measured by the dmft, was significantly different among the maxillary frenulum attachment types (Table 3). Post-hoc analysis revealed that the absence of decay missed, or filled primary maxillary incisors was significantly higher in children with mucosal type frenulum ($p<0.01$). However, the presence of decay, and missed or filled primary maxillary incisors was significantly higher in children with papillary type frenulum ($p<0.01$).

Discussion

The present study indicated that there was a significant association between maxillary labial frenulum attachment types and oral health (periodontal status and dental caries) in pre-school children. There are only a few studies investigating the association between maxillary labial frenulum attachment types and oral health status, including periodontal health and dental caries, among preschool children (15).

The classification method of maxillary labial frenulum attachment may vary in different studies. There are different classifications regarding the categorization of the maxillary labial frenulum (9,16). Sewerin classified the maxillary labial frenulum attachment into 8 types according to anatomical variations and anomalies (16). Placek et al. (9) classified based on the relationship between the maxillary labial frenulum and the periodontium of maxillary incisors. This more practical classification method has gained wide acceptance and has been commonly used. We also used the classification of Placek et al. (9) that was used in many previous studies including children.

There are many studies investigating the incidence of maxillary frenulum attachment types in children (5,9,17-19). Similar to our results, Boutsi and Tatakis (5) reported that gingival type was the most common maxillary labial frenulum attachment type in their study using the same classification method as our study. In

children, the earliest epidemiologic study about maxillary labial frenulum attachment was published by Bergese (20). Although Bergese (20) used a different classification method, the most prevalent maxillary labial frenulum attachment type was reported as "inserting the attached gingiva", which was consistent with the results of the present study. In previous studies involving older children, it was reported that the mucosal type was the most common maxillary labial frenulum attachment type (9,21).

The frenulum inserted into the gingiva is considered abnormal as it facilitates the development of midline diastema and limits lip movement (22,23). Abnormal frenulum attachments can affect suckling and feeding in infants, as well as they can contribute to the occurrence of dental caries. Kotlow (17) stated that although breastfeeding alone did not cause dental caries, breastfeeding in combination with abnormal maxillary frenulum attachment might be a contributing factor to the development of dental caries in a breastfed infant. Papillary type and papillary penetrating type frenulum in a nursing infant have the potential to cause dental caries, as they abnormally restrict the upper lip and make it difficult to remove residual milk after breastfeeding is complete. In our study, the reason for the higher oral hygiene, PI, and GI scores in children with papillary type and papillary penetrating type frenulum attachment may be the limitation of the normal functions and mobility of the upper lip. Accordingly, the incidence of caries in maxillary incisors increased in children with papillary type and with papillary penetrating type frenulum.

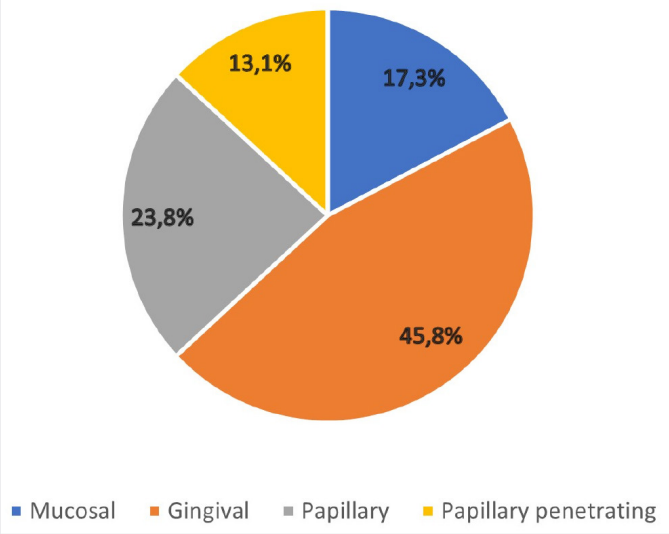

Figure 2. Distribution of maxillary labial frenulum attachment types

Table 2. The association between maxillary labial frenulum attachment types, plaque index, and gingival index scores

	Maxillary labial frenulum attachment types	Median (interquartile range)	P-value*
PI	Mucosal[A]	0.13 (0.00-0.50)	0.01
	Gingival[B]	0.75 (0.25-1.00)	
	Papillary[C]	1.38 (1.00-1.88)	
	Papillary penetrating[C]	2.00 (1.50-2.09)	
GI	Mucosal[A]	0.00 (0.00-0.25)	0.01
	Gingival[B]	0.75 (0.13-1.00)	
	Papillary[C]	1.00 (0.75-1.38)	
	Papillary penetrating[C]	1.50 (1.00-1.75)	

*P-value less than 0.05 is considered significant using the Kruskal-Wallis test and post-hoc Bonferroni test.
There was significant difference between values with different superscript letters.

Frenal attachments have been considered as contributing to periodontal disease. Glickman (24) suggested that the frenulum, attached to the gingival margin, pulled the tissue margin away from the tooth and facilitated plaque accumulation. It is thought that plaque scores and the prevalence of gingivitis should increase in children in whom the labial frenulum attachment adheres to the gingival margin (25). This situation may explain our higher PI and GI scores in children with papillary type and with papillary penetrating type frenulum.

In the primary dentition, the physiological diastema between the maxillary incisors facilitates the cleaning of interproximal areas (26). However, abnormal maxillary frenulum attachment may be a contributing factor to decalcification and development of caries in the mesial areas of the maxillary central incisors by making it difficult to clean the interproximal areas. In our study, caries incidence was significantly lower in children with mucosal type frenulum, while it was significantly higher in children with papillary type frenulum. This result may be due to the change in the cleaning functions of the upper lip according to the frenulum type. In this case, it becomes even more important to remove the plaque that accumulates on the teeth by brushing. However, high frenal attachments such as papillary type or papillary penetrating

Table 3. The association between maxillary labial frenulum attachment types and dental status (dmft) of primary incisors

Maxillary labial frenulum attachment types	dmft		P-value*
	<1	≥1	
Mucosal	21[A]	16[B]	0.01
Gingival	36[A]	62[A]	
Papillary	4[A]	47[B]	
Papillary penetrating	6[A]	22[A]	

*P-value less than 0.05 is considered significant using chi-squared test and post-hoc Bonferroni test.
There was significant difference between values with different superscript letters.

type may complicate the patient's ability to remove plaque. Plaque control should be carefully monitored especially in young children with limited toothbrushing ability.

Study Limitations

The growth of the alveolar process in the coronal direction causes the apical migration of the frenulum attachment. As age progresses, the frenulum attachment may move from a more coronal position to a more apical position (27). Determining the age ranges more limited may provide a clearer determination of the placement of frenulum attachments in further studies. In addition, the possible relationship between maxillary labial frenulum attachment types and oral health will be clearly understood with further studies in which more children will be included.

Conclusion

In conclusion, this study's results showed that the most common maxillary frenulum attachment type in preschool children was the gingival type, while the papillary penetrating type was the least common. Papillary type and papillary penetrating type frenulum attachments were associated with a decline in periodontal health and higher caries incidence in maxillary primary incisors. In clinical examination, the type of maxillary labial frenulum attachment should be evaluated in terms of possible oral health problems.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Research Ethics Committee of Bezmialem Vakıf University in full accordance with the ethical principles of the Helsinki Declaration (protocol no: 04.11.2020-12/24).

Informed Consent: Written informed consent from the parents and verbal assent from the children were also obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: P.K.T., B.A., H.Y., Concept: D.K.T., Design: D.K.T., Ş.Ö., Data Collection or Processing: B.A., H.Y.A., Analysis or Interpretation: D.K.T., Ş.Ö., Literature Search: D.K.T., Ş.Ö., Writing: D.K.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Gartner LP, Schein D. The superior labial frenum: a histologic observation. Quintessence Int 1991;22:443-5.
2. Moore KL, Persaud TVN. The Developing Human: Clinically Oriented Embryology. Philadelphia, PA: Saunders; 2008.
3. Priyanka M, Sruthi R, Ramakrishnan T, Emmadj P, Ambalavanan N. An overview of frenal attachments. J Indian Soc Periodontol 2013;17:12-5.
4. Mintz SM, Siegel MA, Seider PJ. An overview of oral frena and their association with multiple syndromes and nonsyndromic conditions. Oral Surg Oral Med Oral Pathol Oral Radio/Endo 2005;99:321-4.
5. Boutsi EZ, Tatakis DN. Maxillary labial frenum attachment in children. Int J Paediatr Dent 2011;21:284-8.
6. American Academy of Pediatric Dentistry. Policy on Management of the Frenulum in Pediatric Dental Patients. The Reference Manual of Pediatric Dentistry 2019;66-70.
7. Minsk L. The frenectomy as an adjunct to periodontal treatment. Compend Contin Educ Dent 2002;23:424-6, 428.
8. American Academy of Pediatric Dentistry. Policy on early childhood caries (ECC): Classifications, consequences, and preventive strategies. The Reference Manual of Pediatric Dentistry 2020;79-81.
9. Placek M, Skach M, Mrklas L. Significance of the labial frenum attachment in periodontal disease in man. Part I. Classification and epidemiology of the labial frenum attachment. J Periodontol 1974;45:891-4.
10. Webb AN, Hao W, Hong P. The effect of tongue-tie division on breastfeeding and speech articulation: A systematic review. Int J Pediatr Otorhinolaryngol 2013;77:635-46.
11. Santa Maria C, Aby J, Truong MT, Thakur Y, Rea S, Messner A. The Superior Labial Frenulum in Newborns: What Is Normal? Glob Pediatr Health 2017;4:2333794X17718896.
12. Silness J, Loe H. Periodontal disease in pregnancy II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964;22:121-35.
13. Loe H, Silness J. Periodontal disease in pregnancy I. Prevalence and severity. Acta Odontol Scand 1963;21:533-51.
14. World Health Organization. Oral health surveys, basic methods. Geneva: World Health Organization; 1997.
15. Güler Ş, Güler D, Öğütçü U. Labial Frenulum Types and Their Effects on Gingival Health in Children Living in and Around Bolu. Anadolu Klin 2020;25:108-11.
16. Sewerin I. Prevalence of variations and anomalies of the upper labial frenum. Acta Odontol Scand 1971;29:487-96.
17. Kotlow LA. The influence of the maxillary frenum on the development and pattern of dental caries on anterior teeth in breastfeeding infants: prevention, diagnosis, and treatment. J Hum Lact 2010;26:304-8.
18. Rajani ER, Biswas PP, Emmatty R. Prevalence of variations in morphology and attachment of maxillary labial frenum in various skeletal patterns - A cross-sectional study. J Indian Soc Periodontol 2018;22:257-62.
19. Díaz-Pizán ME, Lagravère MO, Villena R. Midline diastema and frenum morphology in the primary dentition. J Dent Child (Chic) 2006;73:11-4.
20. Bergese F. Research on the development of the labial frenum in children of age 9–12 (in Italian). Minerva Stomatol 1966;15:672-6.
21. Jańczuk Z, Banach J. Prevalence of narrow zone of attached gingiva and improper attachment of labial frena in youths. Community Dent Oral Epidemiol 1980;8:385-6.
22. Bresslin WW. Excision of the abnormal frenum. J Can Dent Assoc 1949;15:20.

23. Fischer TJ, Psaltis GL. The diastema and the abnormal frenum. ASDC J Dent Child 1981;48:264-8.

24. Glickman I. Clinical Periodontology, Philadelphia, London and Toronto: W. B. Saunders Co; 1972.

25. Addy M, Dummer PM, Hunter ML, Kingdon A, Shaw WC. A study of the association of fraenal attachment, lip coverage, and vestibular depth with plaque and gingivitis. J Periodontol 1987;58:752-7.

26. Huang WJ, Creath CJ. The midline diastema: a review of its etiology and treatment. Pediatr Dent 1995;17:171-9.

27. Popovich F, Thompson GW, Main PA. The maxillary interincisal diastema and its relationship to the superior labial frenum and intermaxillary suture. Angle Orthod 1977;47:265-71.

Original Article

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Fatal Poisonings: Autopsy-Based Study

Ölümcül Zehirlenmeler: Otopsi Temelli Çalışma

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ABSTRACT

Objective: Poisoning is an important public health problem. This study aimed to investigate the demographic characteristics, toxic agents causing death, and the cause of exposure in victims who died due to poisoning.

Methods: In this autopsy-based retrospective study, the demographic data, exposure to toxic substances, cause of death, and date and place of death of victims who died due to poisoning between January 2011 and December 2020 were recorded.

Results: A total of 90 fatal poisoning cases were investigated. The majority of the victims were male (n=69, 76.7%) with a mean age of 43.2±21.5 years. While 13 (14.4%) patients were younger than 18 years old, 14 (15.6%) were 65 years or older. The majority of deaths occurred at the scene (54.4%) and during the winter season (37.8%). While accidental exposure (41.1%) was the most common cause, suicide (31.1%) was the second. Carbon monoxide (CO) was the main toxic agent causing death, followed by the use of prescription drugs and illicit drugs.

Conclusion: CO is the most common cause of death, and the vast majority of victims were exposed by accident. It is important to educate the public and take the necessary precautions in reducing these deaths. Prescription drugs and illicit drugs were other common causes of death, respectively.

Keywords: Fatal, poisoning, autopsy

ÖZ

Amaç: Zehirlenmeler önemli bir halk sağlığı sorunudur. Bu çalışmada zehirlenme sonucu ölen mağdurların demografik özellikleri, ölüme neden olan toksik ajanlar ve maruziyet nedenlerinin araştırılması amaçlanmıştır.

Yöntemler: Otopsiye dayalı bu retrospektif çalışmada, Ocak 2011-Aralık 2020 tarihleri arasında zehirlenme nedeniyle ölen mağdurların demografik verileri, maruz kalınan toksik maddeler, ölüm nedenleri, ölüm tarihleri ve yerleri kaydedildi.

Bulgular: Toplam 90 ölümcül zehirlenme olgusu araştırıldı. Mağdurların çoğunluğu erkekti (n=69, %76,7) ve yaş ortalaması 43,2±21,5'ti. Hastaların 13'ü (%14,4) 18 yaşından küçükken, 14'ü (%15,6) 65 yaş ve üzerindeydi. Ölümlerin çoğu olay yerinde (%54,4) ve kış mevsiminde (%37,8) meydana geldi. Ölüme en sık kaza sonucu maruz kalma (%41,1) neden olurken, intihar (%31,1) ikinci sıradaydı. Ölüme neden olan başlıca toksik ajan karbonmonoksitti (CO), bunu reçeteli ilaç ve yasa dışı uyuşturucu kullanımı izledi.

Sonuç: CO en yaygın ölüm nedenidir ve kurbanların büyük çoğunluğu kaza sonucu maruz kalmıştır. Bu ölümlerin azaltılmasında halkın eğitilmesi ve gerekli önlemlerin alınması önemlidir. Reçeteli ilaçlar ve yasa dışı uyuşturucular sırasıyla diğer yaygın ölüm nedenleriydi.

Anahtar Sözcükler: Ölümcül, zehirlenme, otopsi

Introduction

Poisoning, one of the leading causes of emergency department presentations, is a public health problem that can cause significant morbidity and mortality worldwide (1-3). Deaths related to acute poisoning may occur due to accidents, suicides (intentional), and substance use disorders (4-6). The agents causing poisoning

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vary depending on many factors such as geography, accessibility, socio-economic conditions, and cultural and religious influences (7). Detection of toxic agents that cause deadly poisoning is important to prevent poisoning-related deaths, take additional preventive measures, and provide effective care. Within this scope, this study aimed to identify the toxins that led to fatal poisoning in our region and to present the demographic characteristics of the patients. The results obtained from the study might be useful in preventing deaths caused by poisoning in our region.

Methods

In Turkey, poisoning cases are considered judicial cases. In poisoning-related deaths, a medicolegal autopsy is performed and a scan is made for possible toxins. This retrospective study was carried out by examining the post-mortem records of the cases that had medicolegal autopsy due to poisoning by the Forensic Medicine Institution of Fırat University between January 2011 and December 2020. Cases whose definite cause of death was poisoning as a result of corpse examination, autopsy, and toxicological and pathological examination were included in the study. All deaths due to poisoning occurring inside and outside of the hospital in the aforementioned period were included. Patients' age, gender, exposure to substances, autopsy findings, cause, date, and place of death were recorded. Toxicological test results at the time of admission to the hospital and in the forensic report were recorded. Alcohol, medications, illicit drug levels, blood, and urine samples were studied with ADVIA 1800 Chemistry System (Germany) and commercial kits in hospital admissions. Carboxyhemoglobin levels were measured using the Radiomater ABL AQT90 flex blood-gas analyzer (Denmark). Blood and urine samples for postmortem drugs and pesticides were purified with Solid Phase Extraction Method using OASIS HLB cartridges and the active substances were measured in liquid chromatography-mass spectrometry (LC-MS) and GC-MS (GC-MS) devices. Alcohol and volatile gases in biological fluids were analyzed by headspace-GC (HS-GC) technique. Corrosive substances were analyzed by wet methods such as acid-base methods and anion-cation analysis. Toxic agents were divided into seven groups: Carbonmonoxide (CO), prescription drugs, illicit drugs, alcohol, pesticides, volatile gases and corrosive materials. Since this study was retrospective, patient consent was not obtained. The study was conducted in accordance with the Helsinki Criteria. Ethics committee approval was obtained for the study (22.09.2021-3772).

Statistical Analysis

Statistical Package for the Social Sciences (SPSS 22, Chicago, IL, USA) was used for statistical analysis. The independent samples t-test was used to compare continuous variables while Pearson's $\chi 2$ test was used for categorical variables. Results were presented as numbers, percentages, mean, minimum (min), and maximum (max) values.

Results

A total of 90 fatal poisoning cases were included in this autopsy-based retrospective study. Most of the deaths due to poisoning were male (n=69, 76.7%) and the mean age was 43.2±21.5 years. While only one of the victims was a foreign national (Syrian), the majority of them were from Elazığ (n=61). Others were mostly from nearby provinces [Tunceli (n=9), Bingöl (n=4), Ankara (n=2), Adana (n=2), Muş (n=2), Erzurum (n=1), Erzincan (n=1), Van (n=1), Şırnak (n=1), Diyarbakır (n=1), Şanlıurfa (n=1), Osmaniye (n=1), Ordu (n=1), İstanbul (n=1)].

When the occupations of the deceased were examined, most of them were not working (13 children, 21 unemployed, 14 housewives). While 12 people were self-employed, 8 people were public employees. The occupations of the remaining 22 people could not be determined.

Most deaths occurred in winter (37.8%), followed by summer (22.2%), autumn (21.1%), and spring (18.9%), respectively. CO poisoning was the main cause of death during the winter months. The distribution of toxic agents causing death by seasons and years is shown in Figures 1 and 2.

While approximately half of the deaths (n=49, 54.4%) occurred at the pre-hospital crime scene, 9 (10%) were brought to the emergency department withcardiopulmonary arrest and died there. Additionally, 32 patients (35.6%) died in the service or intensive care unit.

While there was accidental exposure in 42.3% of the victims, 31.1% died due to suicide and 23.3% due to substance abuse. Three patients (3.3%) died due to adverse reactions related to medical applications. While the cause of death was anaphylaxis because of parenteral antibiotic use in two patients, it was neuroleptic malignant syndrome that developed due to antiparkinsonian drug use in one patient. The majority of deaths (80%) involved exposure to a single toxic agent.

The most common cause of death was CO poisoning (36.7%, n=33). While only one of these patients committed suicide, the others had accidental exposure. The mean carboxyhemoglobin saturation of the victims was 52.2±17.1% (min 12, max 82). Most of the CO poisonings were caused by coal stoves (n=17, 51.6%), followed by fire (n=5, 15.2%), natural gas (n=4, 12.1%), charcoal (n=3, 9.1%), and water well (n=2, 6.1%), respectively. In 2 patients, the cause could not be determined.

The use of prescription drugs (30%, n=27) was the second most common cause of death. Ten of these patients had multiple prescription drug intake, 10 had a single prescription drug intake, and seven had illicit drug and/or alcohol intake in combination with the medical drug. While most of the patients (55.6%) took drugs for suicidal purposes, 33.3% used them due to addiction and 11.1% used them due to medical purposes. Ten of the patients (37%) had a known history of psychiatric illness or substance abuse.

The third most common cause of death was illicit drugs (10%). All of the victims had a history of substance abuse.

Alcohol was detected in 8.9% of the deaths due to poisoning. Ethanol was detected in 5 victims. While only 1 took ethanol alone, 2 of them were accompanied by illicit drugs, 1 of them

methanol and 1 prescription drug use. Toxic agents detected in poisoning deaths are given in Table 1.

Considering the route of exposure to the agent, 43.3% were oral, 42.2% were inhalative, and 6.7% were parenteral exposures. In 5.6% of the cases, the route could not be identified. There was both oral and parenteral exposure in 1 case (1.1%).

There were 13 patients (14.4%) aged 18 years and younger, and most of them (n=9, 69.2%) had accidental exposure. Six of the victims died due to CO poisoning, 3 due to pesticide poisoning, 2 due to illicit drugs, 1 due to butane, and 1 due to medical applications.

Table 1. Toxic agents detected in poisoning deaths

Toxic agents	n (%)
Carbon monoxide	33 (36.7)
Prescription drugs	27 (30)
o Benzodiazepines	7 (7.8)
o Opioids	6 (6.7)
o Antidepressant drugs	6 (6.7)
• SSRI	4 (4.4)
• TCA	2 (2.2)
o Antipsychotic	5 (5.6)
o Beta blocker	4 (4.4)
o Antiepileptic	4 (4.4)
o NSAID	4 (4.4)
o Paracetamol	1 (1.1)
o Other drugs*	6 (6.7)
Illicit drugs	9 (10)
o Cannabinoid	6 (6.7)
o Amphetamine	5 (5.6)
Alcohol	8 (8.9)
o Ethanol	4 (4.4)
o Methanol	3 (3.3)
o Ethanol + methanol	1 (1.1)
Pesticides	8 (8.9)
o Organophosphates	3 (3.3)
• Dimethoate	2 (2.2)
• Chlorpyrifos	1 (1.1)
o Aluminum phosphide	2 (2.2)
o Cypermethrin	1 (1.1)
o Fenpyroximate	1 (1.1)
o Unknown	1 (1.1)
Volatile gases (butane, propane, toluene)	7 (7.8)
Corrosive material	5 (5.6)

NSAID: Non-steroidal anti-inflammatory drug, SSRI: Selective Serotonin Reuptake Inhibitor, TCA: Tricyclic antidepressant,
*Clopidogrel, colchicine, pramipexole, pregabalin, metformin

There were 14 patients (15.6%) aged 65 and over, and 11 (78.6%) of them had accidental exposure. While CO was the most common toxic agent in 9 patients, it was pesticides in 2 patients, prescription drugs in 2 patients, and exposure to corrosive substances in 1 patient.

Discussion

Poisoning, which is a serious problem throughout the world, continues to be an important health issue in Turkey. In this retrospective study, a total of 90 fatal poisoning cases that took place over a 10-year period in the province of Elazığ in eastern Turkey were examined. The socio-economic level of the region where the research was conducted was moderate. In our study, most of the victims were male (n=69, 76.7%) and their mean age was 43.2±21.5. In previous studies, similar to our study, the mortality rates were reported to be higher in males (8-11) and young people were more likely to be victims (2).

Previous studies showed that in most fatal poisonings, the victims were found dead at the scene (5,12). In our study, we found that 54.4% of the victims were found dead at the scene, and 10% were brought to the emergency department with cardiopulmonary arrest and died there. The most important factor in reducing these deaths was prevention (12). The remainder of the deaths occurred in the service or intensive care unit.

In a study examining poisoning cases in Turkey between 1923 and 2019, the most common causes of poisoning in Turkey were found to be by accident and for the purpose of suicide (13). In our study, we found that poisoning-related deaths mainly occurred as a result of accident (42.3%) and suicidal intake (31.1%). Victims aged 18 and under as well as victims aged 65 and over had a higher accidental exposure rate (69.2% and 78.6%, respectively).

In the current study, the most important toxic agent causing death was CO, followed by prescription drugs and illicit drugs. Toxic agents that cause deadly poisoning are affected by many factors and vary between countries and change over time. In a study examining fatal poisonings in South India between 2000 and 2006, it was reported that 92.9% of the victims were self-poisoned, and organophosphate compounds (68.7%) were the most common toxic agent causing death (3). In another study examining fatal poisonings that took place in Finland between 2004 and 2009, antidepressants and opioids were found to be the most common medicinal substances causing death (11). A study examining poisoning deaths in Brazil between 2009 and 2013 reported that 50.8% of deaths occurred due to unintentional intake; the main active ingredients were drugs (49.4%), followed by pesticides (29.9%) (8). Additionally, 76.1% of poisoning-related deaths involving 689 cases in northern Finland between 2007 and 2011 were unintentional exposure, and ethanol was the most common poisoning agent (12). In their study in which they analyzed the data of the American College of Medical Toxicology between 2010 and 2016, Friedman et al. (14) reported that 72.7% of fatal poisoning cases had suicidal exposure and most of the deaths (65.3%) were related to pharmaceutical agents.

In a few previous studies in Turkey, similar to our results, CO was shown to be the most common toxic agent causing fatal poisonings (9,10,15,16), whereas pesticides were the most common agents in one study (17). It was reported that almost all of the deaths caused by CO poisoning in Turkey occurred as a result of accident and most frequently in the winter months (9,10,15,16). While only one of the cases with CO poisoning in our study was due to intentional exposure, the remaining 32 cases were unintentional deaths from coal stoves, water heaters, fire, indoor charcoal use, and water wells. The use of coal stoves for heating in winter, fires, gas water heaters, and indoor barbecues are the main causes of CO poisoning (10,11,15,16). The use of CO sensors, appropriate ventilation, and training programs can help prevent CO poisonings (10,18).

The use prescription drugs (30%) was the second most common cause of death, and most of the patients (55.6%) had taken them for suicidal purposes. Drug-induced poisoning is a common problem worldwide, and the active ingredients vary according to the regions (19). It has been reported that 1% of emergency service admissions and 0.2% of forensic autopsies are due to medical drugs (20). In their study, in which they examined cases that presented to the emergency department and resulted in death due to overdose, Friedman et al. (14) reported that non-opioid analgesics were the main agents, followed by opioids, cardiovascular drugs, sedatives, antipsychotics, antidepressants, and sympathomimetics. On the other hand, Lapatto-Reiniluoto et al. (11) reported that antidepressants and opioids were the most common medicinal substances leading to death in Finland. The main prescription drugs responsible for death in our study were benzodiazepines, opiates, and antidepressants. Similar to our study, Battal et al. (16) reported that the most common prescription drug causing death was benzodiazepines, followed by antidepressants and analgesics. Birincioglu et al. (10)

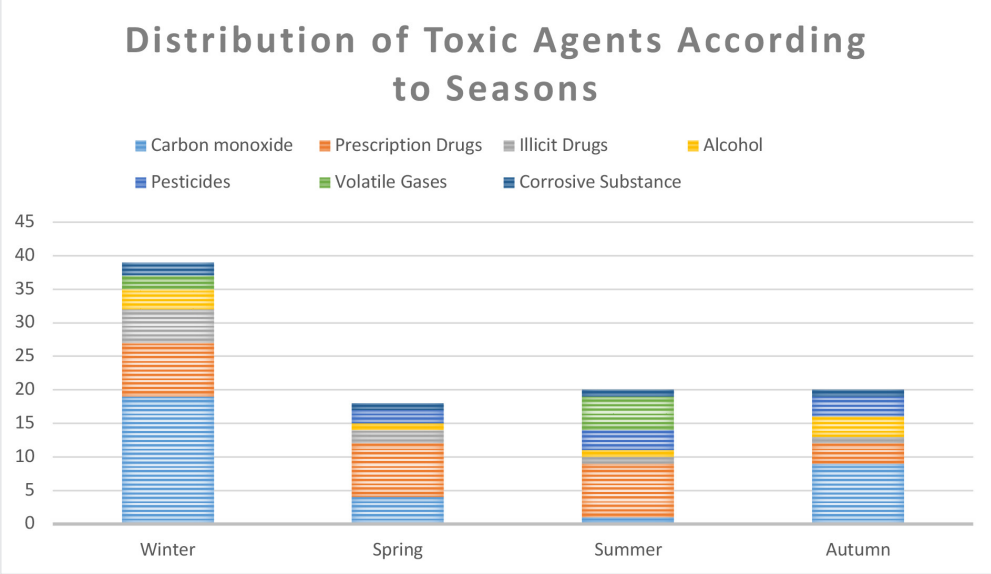

Figure 1. Distribution of toxin agents by seasons

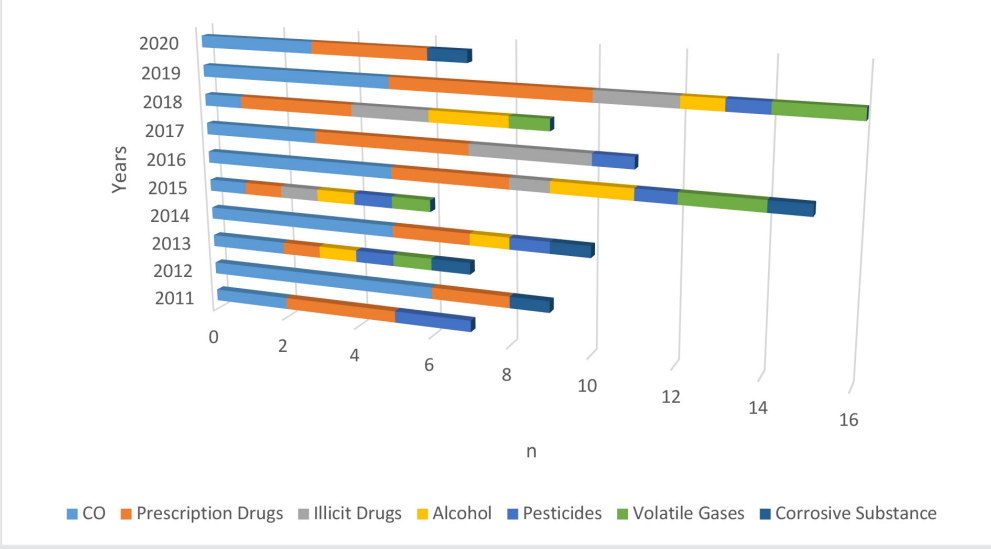

Figure 2. Distribution of toxic agents by years

also reported that fatal drug poisonings mainly occur due to antidepressants and benzodiazepines.

The use of illicit drugs was the third most common cause of death. Although deaths due to substance use disorder are generally thought to occur as a result of accident, the actual intent is unclear (5). All of the victims in our study had a history of substance abuse.

Pesticides were responsible for 8.9% (n=8) of the deaths and most of them were exposed by accident (n=5). Since pesticides are widely used in agriculture, it is one of the common causes of chemical poisoning (3,9). Pesticides are associated with high rates of poisoning, both intentional and accidental, due to reasons such as being applied without adequate protection and being cheap and easy to find (9,10).

Alcohol was detected in 8.9% of the victims. Four of them had drunk ethyl alcohol, 3 had drunk methyl alcohol, and one had drunk both ethyl and methyl alcohol. Alcohol-related death rates vary between countries. In studies conducted in Turkey, rates ranged from 7.4% to 18.4% (9,10,16,19). In our study, 2 of the 4 patients who died due to methyl alcohol had drunk fake or illegally produced alcohol and one had drunk cologne. The substance could not be detected in 1 case. Fake or illegally produced alcohol consumption is an important social problem and it is important to inform society about the dangers of fake alcohol consumption to be able to prevent these deaths. Ethyl alcohol alone caused death in only 1 of the 5 victims. In the others, prescription drugs, illicit drugs or methyl alcohol were taken together with ethyl alcohol.

Volatile gases (butane, toluene, propane) were responsible for 7.8% of deaths and all were intentional exposures. Four of those who died were drug addicts.Volatile substances act quickly, have pleasant and slightly intoxicating effects. It is widely used in society because it is cheap and easy to find, and it continues to be an important public health problem (21).Volatile substance abuse is associated with an increased risk of sudden death, and asphyxia, vagal inhibition, cardiac dysrhythmia, and respiratory depression that can be mortal (22).

Exposure to corrosive substances may be accidental or suicidal. After ingestion, it causes significant damage to other systems, especially the gastrointestinal tract, and may even cause death (23,24). In our study, while 4 of the deaths due to corrosive substances were intentional, 1 was accidental and they were responsible for 5.6% of the deaths.

Study Limitations

Since our study is a retrospective study, missing data may have been entered.

Conclusion

In our study, deaths due to poisoning mostly occurred in males, and the most common causes of exposure were by accident and for the purpose of suicide. CO was the most common fatal toxin, and almost all victims were exposed by accident, and exposures occurred mostly during the winter season. It is important to provide trainings and take necessary precautions to reduce these deaths. It was noteworthy that some medications were also used for suicidal purposes.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Helsinki Criteria. Ethics committee approval was obtained for the study (22.09.2021-3772).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G., A.T., T.B., M.Ç.G., Concept: M.G., N.H.F., T.B., M.A., E.G., Design: M.G., V.G., M.Ç.G., M.A., Data Collection or Processing: M.G., N.H.V., A.T., T.B., V.G., Analysis or Interpretation: M.G., A.T., T.B., M.A., E.G., Literature Search: M.G., N.H.V., T.B., V.G., M.Ç.G., E.G., Writing: M.G.

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References

1. Thapa S, Dawadi BJ, Upreti AJ. Acute Poisoning among Patients Presenting to the Emergency Department of a Tertiary Care Center: A Descriptive Cross-sectional Study. J Nepal Med Assoc 2020;58:470-3.
2. Sawicka E, Kartuszyńska P, Kuczyńska H, Piwowar A. A Retrospectıve Observatıonal Study On Patients Intoxicated By Drugs And Other Xenobıotics. Int J Occup Med Environ Health 2019;32:489-501.
3. Kanchan T, Menezes RG, Kumar TSM, Bakkannavar SM, Bukelo MJ, Sharma PS et al. Toxicoepidemiology of fatal poisonings in Southern India. J Forensic Leg Med 2010;17:344-7.
4. Lindqvist E, Edman G, Hollenberg J, Nordberg P, Ösby U, Forsberg S. Intensive care admissions due to poisoning. Acta Anaesthesiol Scand 2017;61:1296-304.
5. Bjornaas MA, Teige B, Hovda KE, Ekeberg O, Heyerdahl F, Jacobsenet D. Fatal poisonings in Oslo: a one-year observational study. BMC Emerg Med 2010;10:13.
6. Koskela L, Raatiniemi L, Bakke HK, Ala-Kokko T, Liisanantti J. Fatal poisonings in Northern Finland: causes, incidence, and rural-urban differences. Scan J Trauma,Resusc Emerg Med 2017;25:90.
7. Shazia S, Khan MJ, Rashid H, Farooq A, Umair M, Syed SU. Two Years Analysis of Acute Poisoning In Patients Presented To Emergency Department Of Ayub Teachıng Hospital, Abbottabad. J Ayub Med Coll Abbottabad 2020;32:628-32.
8. Steentoft A, Teige B, Ceder G, Kristinsson J, Simonsen KW, Holmgren P, et al. Fatal poisoning in drug addicts in the Nordic countries. Forensic Sci Int 2001;123:63-9.
9. Karaarslan B, Karapirli M, Kandemir E, Kucuker H, Gurler M, Ince CH et al. The Fatal Poisoning Pattern of Ankara (Turkey) and Nearby

Cities from 2007 to June 2011: A Retrospective Study in Forensic Autopsies. J Forensic Sci 2013;58:1563-7.

10. Birincioglu I, Karadeniz H, Teke HY. Fatal Poisonings in Trabzon (Turkey). J Forensic Sci 2011;56:661-3.
11. Lapatto-Reiniluoto O, Vuori E, Hoppu K, Ojanpera I. Fatal poisonings in Finland during the years 2004-2009. Hum Exp Toxicol 2012;32:600-5.
12. Koskela L, Raatiniemi L, Bakke HK, Ala-Kokko T, Liisanantti J. Do pre-hospital poisoning deaths differ from in-hospital deaths? A retrospective analysis. Scand J Trauma Resusc Emerg Med 2017;25:48.
13. Göney G. Analyses of the rates and causes of poisoning in Turkey from 1923 to 2019. Med J SDU 2020;(special issue-1);1-6.
14. Friedman N, Shoshani-Levy M, Brent J, Wax P, Campleman SL, Finkelstein Y. Fatalities in poisoned patients managed by medical toxicologists. Clin Toxicol (Phila) 2020;58:688-91.
15. Dirlik M, Bostancıoğlu B. Deaths due to carbon monoxide poisoning in Aydın, western Turkey. Death Stud 2017;41:246-50.
16. Battal D, Aktas A, Sungur MA, Bilgin NG, Cekin N. Evaluation of poisoning deaths in the Cukurova Region, Turkey, 2007-2011. Toxicol Ind Health 2016;32:476-84.
17. Elif D, Akgür SA, Oztürk P, Sen F. Fatal poisonings in the Aegean region of Turkey. Vet Hum Toxicol 2003:45:106-8.
18. Karapirli M, Kandemir E, Akyol S, Kantarci MN, Kaya M, Akyol O. Forensic and clinical carbon monoxide (CO) poisonings in Turkey: A detailed analysis. J Forensic Leg Med 2013;20:95-101.
19. Fedakar R, Türkmen N. Fatal poisonings in the south marmara region of Turkey, 1996-2003. Eur J Gen Med 2008;5:1-8.
20. Jönsson AK, Spigset O, Tjäderborn M, Druid H, Hägg S. Fatal drug poisonings in a Swedish general population. BMC Clin Pharmacol 2009;9:7.
21. Gürses MS, Aydoğan T, Eren B, Eren F. Death due to Intoxication with Volatile Gases: Retrospective Autopsy Study. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2019;42:125-9.
22. Sasao A, Yonemitsu K, Ohtsu Y, Mishima S, Nishitani Y. Forensic Sci Int 2015;254:180-4.
23. Acehan S, Satar S, Gulen M, Avci A. Evaluation of corrosive poisoning in adult patients. Am J Emerg Med 2021;39:65-70.
24. Swain R, Behera C, Gupta SK. Fatal corrosive ingestion: A study from South and South-East Delhi, India (2005-2014). Med Sci Law 2016;56:252-7.

Original Article

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Physical Activity and Perceptions of Exercise in Patients with Spondyloarthritis: A Cross-Sectional Study

Spondiloartrit Hastalarının Fizik Aktivitesi ve Egzersiz Algısı: Kesitsel Bir Çalışma

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ABSTRACT

Objective: Exercise is a cornerstone in the management of spondyloarthritis (SpA). The aim of this research was to compare the levels of physical activity (PA) and perceived advantages and barriers to exercise of SpA patients with population controls.

Methods: In this cross-sectional study 200 patients (118 males, 82 females) and 100 controls (50 males, 50 females) were included. Levels of PA were evaluated using the International Physical Activity Questionnaire-Short Form and perceptions of exercise were assessed using Exercise Benefits and Barriers Scale. Fatigue, psychological status and quality of life of all participants were questioned. Disease activity, functions and mobility of the patients were also assessed. Correlations were analyzed between disease parameters and perceptions of exercise.

Results: PA levels were similar on both groups. Of the patients 65% met recommended amount of exercise. Deterioration of psychological status and quality of life were associated with decreased PA levels of the patients. Patients reported fatigue and lack of time barriers more than controls. When disease activity, functionality, mobility, fatigue, psychological status and quality of life of the patients deteriorated, perceived barriers to exercise increased.

Conclusion: Health professionals should focus on personal barriers to improve exercise behavior in SpA patients.

Keywords: Spondyloarthritis, physical activity, exercise, motivation

ÖZ

Amaç: Egzersiz spondiloartritlerin (SpA) yönetiminde bir köşe taşıdır. Bu araştırmanın amacı, SpA hastalarının fiziksel aktivite (PA) düzeylerini ve egzersizden algılanan avantajları ve engelleri popülasyon kontrolleriyle karşılaştırmaktır.

Yöntemler: Bu kesitsel çalışmaya 200 hasta (118 erkek, 82 kadın) ve 100 kontrol (50 erkek, 50 kadın) dahil edildi. PA seviyeleri Uluslararası Fiziksel Aktivite Anketi-Kısa Form ile değerlendirildi ve egzersiz algıları Egzersiz Faydaları ve Engeller Ölçeği ile değerlendirildi. Tüm katılımcıların yorgunluğu, psikolojik durumu ve yaşam kalitesi sorgulandı. Hastaların hastalık aktivitesi, fonksiyonları ve mobilitesi de değerlendirildi. Hastalık parametreleri ve egzersiz algıları arasındaki korelasyonlar incelendi.

Bulgular: PA seviyeleri her iki grupta da benzerdi. Hastaların %65'i tavsiye edilen egzersiz miktarını karşıladı. Psikolojik durumun ve yaşam kalitesinin bozulması, hastaların PA düzeylerinin azalması ile ilişkiliydi. Hastalar yorgunluk ve zaman yokluğu bariyerini kontrollere göre daha fazla bildirdi. Hastaların hastalık aktivitesi, işlevselliği, hareketliliği, yorgunluğu, psikolojik durumu ve yaşam kalitesi kötüleştiğinde, egzersizin önündeki algılanan engeller arttı.

Sonuç: Sağlık çalışanları, SpA hastalarında egzersiz davranışını iyileştirmek için algılanan kişisel engellere odaklanmalıdır.

Anahtar Kelimeler: Spondiloartritler, fiziksel aktivite, egzersiz, motivasyon

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Introduction

Spondyloarthritis (SpA) is a family of several inflammatory rheumatic diseases. The prototypic and most studied subtype is ankylosing spondylitis (AS). Spinal (axial) features, peripheral arthritis, enthesopathy, and extra-articular features such as uveitis, psoriasis, and inflammatory bowel disease are among the numerous clinical features (1). The SpA is associated with reduced physical function, poorer quality of life, and irreversible structural damage (2). The treatment goals in SpA are to improve the patient's health (e.g., pain, functional disability) and prevent clinical deterioration and progressive structural damage (1). Current guidelines suggest a mixture of pharmacological and non-pharmacological treatment strategies for the effective care of patients with AS and PsA, in which regular exercise is the key to the non-pharmacological treatment (3). The Cochrane systematic review of AS physiotherapy treatments indicates that home exercise or recreational programs of at least 30 minutes a day, 5 to 7 days a week, are successful in improving discomfort, stiffness and preserving functionality (4).

Physical inactivity has been listed as the fourth leading global mortality risk factor (6% of deaths globally). In addition, a variety of comorbidity conditions such as diabetes mellitus, obesity, hypertension, cancer, and osteoporosis are avoided by regular physical activity (PA), which also decreases the risk of cardiovascular comorbidity. Therefore, the World Health Organization (WHO) recommends at least 150 minutes of moderate-intensity aerobic PA or 75 minutes of vigorous-intensity aerobic PA per week, accumulated in bouts of 10 minutes or more, in addition to muscle-strengthening activities twice-weekly or more in adults aged between 18 to 64 years (5).

Despite the growing evidence supporting the importance of exercise in the management of AS, a large proportion of patients are less active than recommended (6-8). Personal, social, and environmental factors affect PA participation (9). Personal factors include expected benefits and barriers to exercise. Barriers to PA (e.g., lack of time, too tiring, no facilities, lack of exercise partner) strongly influence exercise behavior (10). The main objective of this research was to define levels of PA and perceived advantages and barriers of exercise in patients with SpA and compare the results with population controls. The secondary aim was to investigate the relationships between exercise perceptions and demographic characteristics, medications, disease activity, function, mobility, psychological status, and quality of life.

Methods

Patients attending outpatient clinics of physical medicine and rehabilitation and rheumatology departments of a university hospital and population controls were recruited for this cross-sectional comparative study. The research was conducted between March and July 2014. Ethical approval was obtained from the Bezmialem Vakıf University's Clinical Research Ethics Committee (approval number: 71306642/050-01-04/81), and all participants signed informed consent. All patients who met the Assessment of Spondyloarthritis International Society (ASAS) criteria for SpA were considered for inclusion. In addition, population controls matching for gender and age were recruited. Eligibility criteria included the age of 18 to 65 and the ability to understand a questionnaire, willing to fill out a questionnaire. Participants were excluded if they had a concurrent cardiac, respiratory or neurological disorder or comorbidity restricting their exercise capacity.

Demographic characteristics including age, gender, body mass index (BMI), education (year of education), employment status (employed or not), marital status, and smoking history were collected.

Disease characteristics: Clinical variables including disease duration, time since diagnosis, and primary pharmacological managements [non-steroidal anti-inflammatory drugs, sulphasalazine, or anti-tumor necrosis factor (TNF) therapy] of the patients were questioned. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were recorded from the laboratory analyses.

Bath AS Disease Activity Questionnaire (BASDAI), AS Disease Activity Score-Erythrocyte Sedimentation Rate (ASDAS-ESR), and ASDAS-CRP were calculated and recorded to determine the disease activity. BASDAI consists of six questions (fatigue, spinal pain, joint pain or swelling, localized tenderness areas, severity, and duration of morning stiffness) with a 10 cm visual analog scale (VAS). Lower scores indicate less active disease (11). ASDAS-ESR and ASDAS-CRP were calculated with the formula chosen by the ASAS group (7,8). ASDAS scores calculated from BASDAI questions 2, 3, and 6, patient global assessment of disease activity, and CRP (mg/L) for ASDAS-CRP or ESR (mm/h) for ASDAS-ESR (8). Higher values indicate higher disease activity. Cut-off values have been defined as follows; <1.3 inactive disease, 1.3-2.1 moderate disease activity, 2.1-3.5 high disease activity, and >3.5 very high disease activity.

Patients' functional status was evaluated with Bath Ankylosing Spondylitis Functional Index (BASFI) consisting of ten questions (eight questions regarding everyday tasks, two questions testing patient's capacity of coping with daily life) over the past week using a 10 cm VAS, from no limitations (0 cm) to very severe functional limitation (10 cm). Higher scores indicate more severe impairment (12). Both indices were validated to the Turkish language (13,14).

Bath AS Metrology Index (BASMI) assessed mobility, comprised of tragus to wall distance, modified Schober test, cervical rotation, lateral spinal flexion, and intermalleolar distance (15). Higher scores indicate more restricted mobility.

Total back pain score and nocturnal back pain score were assessed with VAS. Fatigue was also measured with VAS by the question, "How would you describe the overall level of fatigue you experienced last week?"

Physical activity: PA levels were evaluated with the International PA Questionnaire-Short Form (IPAQ-S). This self-reported questionnaire was validated in Turkish (16). Volunteers were

asked to remember the number of days, hours, and minutes they spent in PA last week. PA duration of 10 minutes or above was included in the analyses. Energy consumption was expressed as metabolic equivalent (MET) multiplied with time in minutes per week (MET*minutes*week). One MET is the energy consumed at rest, while 3.3 MET is the energy consumed during moderately fast walking, which is 3.3 times higher than at rest. Energy expenditure is 4 MET at moderate PA and 8 MET at vigorous PA. Volunteers were categorized as low, moderate, or high P.A. groups according to their MET*min*week scores.

Exercise profile: The participants' exercise types and frequency were questioned with open-ended questions. Duration of exercise was recorded for the most reported exercise types. The authors compiled the following list according to the most reported activities: Walking, stretching exercises, weight training (including bodybuilding), swimming, football, and other aerobic exercises (e.g., fitness, pilates). Participants were categorized as "met recommended amounts of exercise" if they performed at least 150 minutes of moderate-intensity aerobic-PA or 75 minutes of vigorous-intensity aerobic-PA per week (according to WHO recommendations) (5).

Perceptions of exercise: Exercise perceptions were assessed with the Exercise Benefits and Barriers Scale (EBBS), a well-validated questionnaire initially developed in healthy individuals (17). It is also validated in the elderly population (18), and despite not being validated in chronic diseases, it has been used in many rheumatologic diseases, including AS (6,19). The scale includes 29 benefit items in 5 categories (physical performance, preventive health, psychological outlook, social interaction, and life enhancement) and 14 barrier items in 3 categories (physical exertion, time expenditure, and exercise environment). Respondents rate their agreement with each item on a Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). Possible total scores range from 43 to 172; barrier items are reverse coded, so higher scores suggest a more favorable view of exercise. Distinct subscores for perceived benefits and perceived barriers range from 29 to 116 and 14 to 56, respectively; higher scores suggest more excellent knowledge of either the benefits or barriers. Benefits and barriers subscales were used in this study.

Psychological status: Beck depression scale, a multiple-choice self-report inventory of 21 questions, one of the most frequently used psychometric measures to assess the severity of depression, was used to assess psychological status. The total score is between 0 and 63, and higher scores indicate more severe depression.

Quality of life: Twelve items Short Form health survey (SF-12) was used to assess the quality of life of the patients and control subjects. Twelve questions selected from SF-36 were combined for a simplified questionnaire. The survey consists of two scales of mental and physical functioning and health-related quality of life (MCS, PCS) (20).

Statistical Analysis

In sample size calculation we aimed to compare three groups according to the level of PA. The study population was determined as 159 using G-power program by taking effect size 0.25, alpha=0.05, power (1-beta)=0.89 at a confidence level of 95%. Adding to sample size 25% to compensate for non-response, the number of study group was determined as 200. One hundred participants were included as control group.

The Statistical Package for Social Sciences version 21.0 was used. Variables were presented as frequency and percentage for categorical variables and continuous data were reported as mean and standard deviation. Group differences were examined by chi-square for categorical variables and independent sample t-test for continuous, normally distributed variables. Normal distribution was investigated with Kolmogorov-Smirnov test. Mann-Whitney U test was used for group comparisons since the variables did not show normal distribution. Possible correlations between demographic characteristics and disease parameters with PA, perceived benefits and barriers of exercise were analyzed with Spearman test. A p-value of <0.05 was considered significant.

Results

Of the 268 patients with SpA eligible for the study, 200 (74.6 %) patients agreed to participate. A hundred gender, age and BMI matched controls were included in the study. The mean age of the patients was 38.76±9.60 and control group was 36.51±10.40 (p=0.065). The mean disease duration of the patients was 11.8±8.5 years. Forty-one patients (%20.5) were on anti-TNF therapy. Table 1 presents detailed descriptions of the participants' demographic profiles and disease parameters.

Physical activity (IPAQ): Twenty-nine patients (14.5%) and 14 (14%) of the control subjects were in high PA category. The PA levels of the patients and controls were similar. The PA levels were negatively correlated with BMI and depression, and positively correlated with physical quality of life. PA was not associated to disease activity (BASDAI, ASDAS CRP, ASDAS ESH), functionality, flexibility or anti TNF treatment.

Exercise profiles: One hundred and thirty patients (65%) and 61 (61%) of the controls met the recommended amount of exercise (at least 150 minutes of aerobic PA with moderate intensity or 75 minutes of aerobic PA with vigorous intensity per week) (p=0.495). Walking was most frequently reported type of exercise and walking amounts were similar on both groups. Stretching and other indoor aerobic exercises (fitness and pilates included) were other frequently reported exercises. Among the patients who met the recommended amount of exercise, 65.5% reported walking and 17% reported doing stretching exercises. Among the controls who met the recommended amount of exercise, 70% reported walking and 11% reported doing indoor aerobic exercises regularly (Table 2).

Fatigue scores of the patient and control groups were not different (p=0.907). Patients were significantly more depressed than controls (p=0.001). Patients' physical and mental quality of life scores assessed by SF12 were significantly worse than controls (PCS; p=0.001, MCS; p=0.007). In analysis of the volunteers' perceptions of exercise, patients' and controls' benefits and barriers subscores were similar (p=0.539, p=0.439) (Table 3). Overall, the

most frequently recorded exercise benefits were "Exercise increases my stamina", "Exercise improves my flexibility" and "Exercise increases my muscle strength" in both groups. The most frequently recorded barriers of exercise in patients' group were "Exercise tires me", "I am fatigued by exercise" and "Places for me to exercise are too far away". Control group also reported similar barriers as "Exercise tires me", "I am fatigued by exercise" and "There are too few places for me to exercise". Most frequently reported benefits were on physical performance category and barriers were on physical exertion and exercise environment categories.

On analysis of the correlations between patients' perceptions of exercise with disease parameters, a negative correlation was

Table 1. Demographic characteristics and disease characteristics of the participants

		Patients (n=200)	Controls (n=100)	p-value
Age (years) (mean ± SD)		38.76±9.60	36.51±10.40	0.065
BMI (kg/m²) (meant ± SD)		26.90±4.08	26.16±4.20	0.145
Gender (M/F)		118/82	50/50	0.139
Years of education (mean ± SD)		8.55±3.55	9.9±3.7	**0.002**
Married, n (%)		168 (84)	71 (71)	**0.002**
Employed, n (%)		122 (61)	78 (78)	**0.003**
Smoking history, n (%)		64 (32)	37 (37)	**0.038**
Duration of symptoms (years) (mean ± SD)		11.8±8.5	-	-
Time since diagnosis (years) (mean ± SD)		6.2±6.6	-	-
BASDAI score (mean ± SD)		3.93±2.3	-	-
BASFI score (mean ± SD)		2.95±2.4	-	-
BASMI score (mean ± SD)		2.98±2.2	-	-
ASDAS-CRP (mean ± SD)		2.50±1.02	-	-
ASDAS-ESR (mean ± SD)		2.76±0.97	-	-
Total back pain score (mean ± SD)		4.09±2.9	-	-
Nocturnal back pain score (mean ± SD)		3.86±2.9	-	-
Activity back pain score (mean ± SD)		4.04±2.9	-	-
Patient global score (mean ± SD)		4.08±2.9	-	-
CRP (mg/L) (mean ± SD)		9.76±26.8	-	-
ESR (mm/h) (mean ± SD)		25.07±16.8	-	-
Primary pharmacological management				
	NSAID, n (%)	80 (40)	-	-
	Sulphasalazine, n (%)	79 (39.5)	-	-
	Anti-TNF agent, n (%)	41 (20.5)	-	-
Physical activity (IPAQ-S)		-	-	0.204
	Low, n (%)	47 (23.5)	33 (33)	-
	Medium, n (%)	124 (62)	53 (53)	-
	High, n (%)	29 (14.5)	14 (14)	-

SD: Standard deviation, BMI: Body mass index, M: Male, F: Female, BASDAI: Bath AS Disease Activity Questionnaire, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath AS Metrology Index, ASDAS-CRP: AS Disease Activity Score-C-reactive protein, ASDAS-ESR: AS Disease Activity Score-Erythrocyte Sedimentation Rate

Table 2. Types and minutes of exercise participation of the volunteers last week

	Patients (n=200) (min./week) (mean ± SD)	Controls (n=100) (min./week) (mean ± SD)	p-value
Walking	254.9±292.4	272.3±264.2	0.197
Stretching exercises	51.8±91.9	3.65±23.6	**0.001**
Indoor aerobic exercises	17.5±66.6	32.7±85.5	**0.038**
Weight training	17.9±88.7	15.6±83.1	0.881
Swimming	6.93±32.2	1.2±12	0.062
Football	3±16.7	0.6±6	0.151

min.: Minimum, SD: Standard deviation

found between barriers score with disease activity measured with BASDAI, functional index, depression scores, and fatigue. More negative perception of exercise was correlated with higher disease activity. There was also a positive correlation between barriers score and quality of life. A negative correlation was found between BMI and depression scores with PA. A positive correlation was found between physical quality of life with PA (Table 4).

Patients reported some barriers such as "Exercise tires me" (p=0.004) and "Exercise takes too much time" (p=0.011) more than control subjects. Patients also less frequently reported the benefit "I enjoy exercise" (p=0.04) than controls.

Significant correlations were observed between some questions of EBBS with disease characteristics of the patients. A negative correlation was observed between barrier statements "Exercise tires me", "I am fatigued by exercise" and "Exercise is hard work" with disease activity, functional limitations, lower mobility, depression, fatigue and a positive correlation was observed with quality of life. "Places for me to exercise are too far away" and "Exercise facilities do not have convenient schedules for me" statements were negatively correlated with depression and positively correlated with mental quality of life. A negative correlation was observed between the benefit statement "Exercise gives me a sense of personal accomplishment" with disease activity and depression. "Exercise allows me to continue my normal activities without fatigue" and "I enjoy exercise" statements were also negatively correlated with depression scores (Table 5).

Table 3. Comparison of fatigue and depression scores, quality of life and exercise perceptions of patient and control groups

	Patients (n=200)			Controls (n=100)			
	Mean ± SD	Min.	Max.	Mean ± SD	Min.	Max.	p-value
VAS-fatigue	4.45±3.07	0.0	10	4.15±2.25	0.0	10	0.907
Beck D.	10.81±8.73	0.00	44.00	7.3±6.48	0.00	39.00	**0.001**
SF12 PCS	40.05±9.72	19.60	59.10	48.39±6.98	30.60	60.40	**0.000**
SF12 MCS	45.61±11.02	15.30	67.80	49.33±8.60	29.30	62.50	**0.007**
Benefits EBBS	89.29±12.77	51.00	116.00	88.56±13.35	55.00	114.00	0.539
Barriers EBBS	39.34±5.73	24.00	56.00	40.06±5.7	24.00	56.00	0.439

Min.: Minimum, max.: Maximum; Beck D.: Beck Depression Scale, SF12 PCS: Short Form 12 Physical subscore, SF12 MCS: Short Form 12 Mental subscore. Benefits EBBS: Benefits subscore of Exercise Benefits Barriers Scale, Barriers EBBS: Barriers subscore of Exercise Benefits Barriers Scale

Table 4. The relationship between physical activity and perceptions of exercise of the patients with BMI, fatigue, depression, quality of life, disease activity, functional and mobility indices (Spearman Correlation Analysis)

		Physical activity (IPAQ-S)	Benefits EBBS	Barriers EBSS
BMI	r	**-0.141**	0.101	-0.107
	p	**0.047**	0.156	0.134
VAS-fatigue	r	-0.017	-0.010	**-0.214**
	p	0.811	0.892	**0.002**
Beck D.	r	**-0.143**	-0.077	**-0.158**
	p	**0.046**	0.278	**0.027**
SF12PCS	r	**0.140**	0.006	**0.139**
	p	**0.049**	0.929	**0.050**
SF12MCS	r	0.041	0.092	**0.156**
	p	0.569	0.195	**0.028**
BASDAI	r	-0.032	-0.062	**-0.188**
	p	0.657	0.387	**0.008**
ASDAS-CRP	r	-0.099	-0.112	-0.126
	p	0.167	0.114	0.075
ASDAS-ESH	r	-0.105	-0.120	-0.101
	p	0.139	0.091	0.156
BASFI	r	-0.073	-0.070	**-0.222**
	p	0.305	0.327	**0.002**
BASMI	r	-0.110	0.042	-0.128
	p	0.125	0.551	0.071

Discussion

Regular exercise has clearly numerous benefits. Exercise motivation is affected by many factors such as personal beliefs, cultural or family habits. Effective interventions are required to increase the likelihood of long-term changes in exercise behavior. According to a recent study an intervention should include (1) behavior change guidance, such as individualized education, motivational interviewing, goal setting, action planning, monitoring, and feedback (2) therapist training on how to tailor and practice an exercise program and provide behavior change guidance, and (3) encouragement to exercise in a group, to optimize exercise behavior in people with axSpA (21).

In the present study, 65% of the patients and 61% of the controls met WHO recommendations regarding PA time. In contrast to earlier studies reporting lower PA in axial SpA patients than controls (11,12), our work revealed similar PA levels on both groups. In the literature about PA of SpA patients, the highest rate was from a Swedish study, in which 68% of the patients met the exercise recommendations (22). In a study from France, 55% of the patients with axial SpA met the recommendations (23), and in a study from Canada, this rate was 47.5% (6). In a Norwegian study using the IPAQ, carried out during both summer and winter seasons, 41-61% of patients with axial SpA met health-enhancing PA (7). Our findings were a bit higher than most of the literature results, which reflected cultural differences in exercise methods and our result was similar to Turkish population controls.

Interestingly, in the present study PA of the patients was not associated to SpA features (BASDAI, ASDAS CRP, BASFI, BASMI, or anti TNF treatment). An association between higher disease activity with decreased PA participation was reported in the literature (7,24). In a cross-sectional study conducted on 20 patients with AS with interview technique, it was found that anti-TNF therapy increased the exercise rate and motivation of the patients, and it was thought that this effect was achieved by improving the pain, stiffness fatigue and psychological state of the patients (25). This finding may be consistent with our results, considering the functionality and mobility of the patients on anti-TNF treatment were significantly worse than those who did not use it, the PA levels was similar to others.

Adults with SpA engage in a variety of physical activities. In our group most frequently reported type of exercise was walking. In a study evaluating the effect of walking intervention in patients with AS, improved aerobic capacity and walking distance were found but the intervention did not provide additional benefits in disease activity, functional capacity, mobility and quality of life (26).

Stretching exercises are recommended to maintain spinal mobility in patients with SpA in systematic reviews (27). A study from Canada determined that 33% of patients with SpA regularly engaged in stretching exercises (6). Another study from Sweden concluded that 26% of patients with SpA executed spinal mobility exercises (7). Our findings revealed that 17% of the patients engaged in stretching exercises regularly, which was a bit lower than the literature. The reason for patients performing

Table 5. Significant correlations of some EBBS questions with disease parameters

		BMI	VAS-fatigue	Beck D.	SF12 PCS	SF12 MCS	BASDAI	ASDAS-CRP	ASDAS-ESR	BASFI	BASMI
Exercise tires me	r	**-0.197**	**-0.291**	**-0.221**	**0.288**	**0.211**	**-0.316**	**-0.254**	**-0.226**	**-0.307**	**-0.192**
	p	**0.005**	**0.001**	**0.002**	**0.001**	**0.003**	**0.001**	**0.001**	**0.001**	**0.001**	**0.007**
I am fatigued by exercise	r	-0.138	**-0.252**	**-0.220**	**0.254**	**0.184**	**-0.233**	-0.096	-0.134	**-0.185**	-0.076
	p	0.051	**0.001**	**0.002**	**0.001**	**0.009**	**0.001**	0.178	0.058	**0.009**	0.286
Exercise is hard work	r	-0.116	**-0.159**	**-0.236**	**0.157**	**0.195**	**-0.169**	**-0.148**	**-0.144**	**-0.183**	**-0.140**
	p	0.101	**0.025**	**0.001**	**0.027**	**0.006**	0.017	**0.036**	**0.043**	**0.010**	**0.048**
Exercise facilities do not have convenient schedules for me	r	-0.065	-0.078	**-0.171**	0.001	**0.154**	-0.113	-0.086	-0.025	-0.080	-0.027
	p	0.363	0.273	0.016	0.988	**0.030**	0.111	0.226	0.723	0.258	0.702
Places for me to exercise are too far away	r	-0.122	-0.142	-0.172	0.1	**0.171**	-0.112	-0.102	-0.070	-0.103	**-0.140**
	p	0.085	0.045	0.015	0.161	**0.016**	0.114	0.150	0.324	0.147	**0.047**
Exercise gives me a sense of personal accomplishment	r	0.124	-0.038	-0.129	0.089	0.084	-0.090	**-0.145**	**-0.169**	-0.102	0.054
	p	0.081	0.59	0.071	0.209	0.236	0.206	**0.041**	**0.017**	0.151	0.445
Exercise allows me to continue my normal activities without fatigue	r	0.065	-0.071	**-0.142**	0.053	0.112	-0.077	-0.042	-0.045	-0.021	0.085
	p	0.362	0.32	**0.045**	0.461	0.115	0.280	0.556	0.526	0.769	0.230
I enjoy exercise	r	0.05	-0.081	**-0.164**	0.128	0.135	-0.085	-0.101	-0.075	-0.107	-0.012
	p	0.483	0.252	**0.021**	0.071	0.058	0.230	0.156	0.294	0.130	0.871

BMI: Body mass index, VAS: Visual analog scale, Beck D.: Beck Depression Scale, EBBS: Exercise Benefits and Barriers Scale, PCS: Short Form 12 Physical subscore, Short Form 12 Mental subscore, BASDAI: Bath AS Disease Activity Questionnaire, ASDAS-CRP: AS Disease Activity Score-C-reactive protein, ASDAS-ESR: AS Disease Activity Score-Erythrocyte Sedimentation Rate, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath AS Metrology Index

stretching exercises more than controls might be a result of the emphasis on stretching exercises by health care professionals.

Patients' daily activities accounted for the majority of their PA. Control group had a higher engagement in aerobic activities. Energy expenditure of aerobic exercises such as fitness and pilates (>6 MET) is higher than walking (3.3 MET) and stretching exercises (3.5 MET). Patients should be encouraged to attend higher intensity exercises because of the increased risk for cardiovascular events (28).

Improved physical fitness was reported as the main benefit of exercise by patients as mentioned previously (6,22,29). Fatigue, pain, stiffness and disability were the most frequently reported barriers of patients with SpA in the literature (6,29,30). We found only one study that was comparing exercise perceptions of patients with SpA with population controls (29).The present study showed that higher number of patients with SpA reported fatigue and lack of time and places to exercise as barriers for being physically active than population controls. Also, the benefit item "exercise is enjoying" was less agreed than controls. Since exercise is considered as time consuming by the patients, the family support is essential. Supervision by a health professional who is familiar with both rheumatic diseases and exercise appears to be important. Health professionals should be aware of personal preferences and include them into exercise prescriptions. Furthermore, exercise groups for patients with SpA may help them maintain their exercise routines. During times of increasing symptoms and personal setbacks, social connections among patients with the same disease and similar physical limits may boost motivation to continue exercising (31,32).

As far as we know, this is the first study exploring the effects of disease parameters of patients with SpA on perceived benefits and barriers to exercise. Patients reported "I am fatigued by exercise" and "Exercise is a hard work" as barriers and less reported "I enjoy exercise" and "Exercise gives me a sense of personal accomplishment" as benefits with concordance with higher disease activity, decreased functionality and flexibility. Adherence to PA increases when potential health benefits is understood and as the exercise period progresses, individuals experience increased satisfaction.

Patients reported more barriers about places of exercise while depression and fatigue scores increased and quality of life decreased. Fatigue is an important complaint that impairs the quality of life in patients with SpA. Fatigue in patients with SpA has been shown to decrease by exercise (33). Health care professionals should emphasize the benefits of PA on fatigue in patients with SpA.

A strength of the research was that controls were drawn randomly from the general population to match patients in terms of age, gender and residential area. Barriers to exercise related to disease itself was analyzed.

Study Limitations

The limitations of the study were as follows; barriers and benefits specific to SpA were not identified, but EBBS was used in many rheumatologic diseases (6,19,23) and to our knowledge there was no such a questionnaire specific to SpA population. PA levels were assessed by a self-reported questionnaire (IPAQ-S). There is a tendency to overestimate PA for questionnaires compared with accelerometers (34) but it is a validated questionnaire that has been used previously in many studies and in several countries (7,29).

Conclusion

Heath care professionals may provide improved motivation for patients if they understand why and how they engage in PA. The results of this study suggest we should inform patients regarding the benefits of exercise, make efforts to eliminate perceived barriers to exercise and implement strategies (personal goal setting, monitoring, and feedback etc.) aimed at change of behaviors. Resources (access, time, finances) of exercise for patients should be increased.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Bezmialem Vakıf University's Clinical Research Ethics Committee (approval number: 71306642/050-01-04/81).

Informed Consent: All participants signed informed consent.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: K.G., S.E.D., A.R., T.A., Design: K.G., S.E.D., M.G.G., T.A., Data Collection or Processing: K.G., S.E.D., M.G.G., A.R., Analysis or Interpretation: K.G., S.E.D., M.G.G., A.R., T.A., Literature Search: K.G., S.E.D., A.R., Writing: K.G., S.E.D., M.G.G., A.R., T.A.

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References

1. Dougados M, Baeten D, Spondyloarthritis. Lancet 2011;377: 2127-37.
2. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379-90.
3. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011;70:896-904.
4. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. Cochrane Database Syst Rev 2008;2008:CD002822.
5. World Health Organization, Global recommendations on physical activity for health. 2010 [cited 2017 27.05.2017]. http://apps.who.int/iris/bitstream/10665/44399/1/9789241599979_eng.pdf
6. Passalent LA, Passalent LA, Soever LJ, O'Shea FD, Inman RD. Exercise in ankylosing spondylitis: discrepancies between recommendations and reality. J Rheumatol 2010;37:835-41.

7. Fongen C, Halvorsen S, Dagfinrud H. High disease activity is related to low levels of physical activity in patients with ankylosing spondylitis. Clin Rheumatol 2013;32:1719-25.
8. Sundström B, Ekergård H, Sundelin G. Exercise habits among patients with ankylosing spondylitis. A questionnaire based survey in the County of Västerbotten, Sweden. Scand J Rheumatol 2002;31:163-7.
9. Abazov VM, Abbott B, Abolins M, Acharya BS, Adams M, Adams T, et al. Direct limits on the oscillation frequency. Phys Rev Lett 2006;97:021802.
10. Trost SG, Owen N, Bauman AE, Sallis JF, Brown W. Correlates of adults' participation in physical activity: review and update. Med Sci Sports Exerc 2002;34:1996-2001.
11. O'Dwyer T, O'Shea F, Wilson F. Decreased physical activity and cardiorespiratory fitness in adults with ankylosing spondylitis: a cross-sectional controlled study. Rheumatol Int, 2015;35:1863-72.
12. Swinnen, Scheers T, Lefevre J, Dankaerts W, Westhovens R, de Vlam K. Physical activity assessment in patients with axial spondyloarthritis compared to healthy controls: a technology-based approach. PLoS One 2014;9:e85309.
13. Akkoc Y, Karatepe AG, Akar S, Kirazli Y, Akkoc N. A Turkish version of the Bath Ankylosing Spondylitis Disease Activity Index: reliability and validity. Rheumatol Int 2005;25:280-4.
14. Yanik B, Gürsel YK, Kutlay S, Ay S, Elhan AH. Adaptation of the Bath Ankylosing Spondylitis Functional Index to the Turkish population, its reliability and validity: functional assessment in AS. Clin Rheumatol 2005;24:41-7.
15. Jenkinson, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694-8.
16. Saglam M, Arikan H, Savci S, Inal-Ince D, Bosnak-Guclu M, Karabulut E, et al. International physical activity questionnaire: reliability and validity of the Turkish version. Percept Mot Skills 2010;111:278-84.
17. Sechrist KR, Walker SN, Pender NJ. Development and psychometric evaluation of the exercise benefits/barriers scale. Res Nurs Health 1987;10:357-65.
18. Akbari Kamrani AA, Zamani Sani SH, Fathire-Zaie Z, Bashiri M, Ahmadi E. The Psychometric Characteristics of the Exercise Benefits/Barriers Scale among Iranian Elderly. Iran J Public Health 2014;43:362-6.
19. O'Dwyer, T, Rafferty T, O'Shea F, Gissane C, Wilson F. Physical activity guidelines: is the message getting through to adults with rheumatic conditions? Rheumatology (Oxford) 2014;53:1812-7.
20. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33.
21. Hilberdink B, van der Giesen F, Vlieland TV, Nijkamp M, van Weely S. How to optimize exercise behavior in axial spondyloarthritis? Results of an intervention mapping study. Patient Educ Couns 2020;103:952-9.
22. Haglund E, Bergman S, Petersson IF, Jacobsson LT, Strömbeck B, Bremander A. Differences in physical activity patterns in patients with spondylarthritis. Arthritis Care Res (Hoboken) 2012;64:1886-94.
23. Fabre S, Molto A, Dadoun S, Rein C, Hudry C, Kreis S, et al., Physical activity in patients with axial spondyloarthritis: a cross-sectional study of 203 patients. Rheumatol Int 2016;36:1711-8.
24. Brophy S, Cooksey R, Davies H, Dennis MS, Zhou SM, Siebert S. The effect of physical activity and motivation on function in ankylosing spondylitis: a cohort study. Semin Arthritis Rheum 2013;42:619-26.
25. Stockdale J, Selfe J, Roddam H. An exploration of the impact of anti-TNFα medication on exercise behaviour in patients with ankylosing spondylitis. Musculoskeletal Care 2014;12:150-9.
26. Jennings F, Oliveira HA, de Souza MC, Cruz Vda G, Natour J. Effects of Aerobic Training in Patients with Ankylosing Spondylitis. J Rheumatol 2015;42:2347-53.
27. O'Dwyer T, O'Shea F, Wilson F. Exercise therapy for spondyloarthritis: a systematic review. Rheumatol Int 2014;34:887-902.
28. Mathieu S, Gossec L, Dougados M, Soubrier M. Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis. Arthritis Care Res 2011;63:557-63.
29. Fongen C, Sveaas SH, Dagfinrud H. Barriers and Facilitators for Being Physically Active in Patients with Ankylosing Spondylitis: A Cross-sectional Comparative Study. Musculoskeletal Care 2015;13:76-83.
30. O'Dwyer T, McGowan E, O'Shea F, Wilson F. Physical Activity and Exercise: Perspectives of Adults With Ankylosing Spondylitis. J Phys Act Health 2015;13:504-13.
31. Analay Y, Ozcan E, Karan A, Diracoglu D, Aydin R. The effectiveness of intensive group exercise on patients with ankylosing spondylitis. Clin Rehabil 2003;17:631-6.
32. Bilberg A, Sveaas SH, Dagfinrud H, Mannerkorpi K. How Do Patients With Axial Spondyloarthritis Experience High-Intensity Exercise?. ACR Open Rheumatol 2020;2:207-13.
33. Gossec L, Dougados M, D'Agostino MA, Fautrel B. Fatigue in early axial spondyloarthritis. Results from the French DESIR cohort. Joint Bone Spine 2016;83:427-31.
34. Ainsworth BE. How do I measure physical activity in my patients? Questionnaires and objective methods. Br J Sports Med 2009;43:6-9.

Original Article

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Investigation of Proprioception and Kinesthesia Sensations in the Upper Extremities of Children with Childhood Cancer

Çocukluk Çağı Kanserli Çocukların Üst Ekstremitelerinde Propriosepsiyon ve Kinestezi Duyularının İncelenmesi

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ABSTRACT

Objective: The objective of this study was to examine the proprioception and kinesthesia functions of the upper limbs in children who were undergoing chemotherapy treatment and hospitalized with various cancer diagnoses.

Methods: Two hundred thirteen (101 females, 112 males) children with childhood cancer participated in this study. The proprioception and kinesthesia senses of the upper extremities were evaluated within the hospital setting. The sense of position, which was a clinical assessment, was used to assess proprioception. The kinesthesia subtest of Sensory Integration and Praxis Test was used to evaluate the kinesthesia sense. Kruskal-Wallis test was used to compare mean values according to diagnostic criteria. Spearman's coefficient of correlation was used for bivariate correlations and the statistical significance was accepted as $p<0.05$.

Results: There was no significant difference in proprioception scores and kinesthesia averages according to diagnosis types ($p>0.05$). In proprioception scores, according to diagnosis types, the lowest score was in the carcinoma group, while the highest score was seen in lymphoma group. In terms of kinesthesia, the most affected was the lymphoma group, while the leukemia group was least. In addition, no significant relationship was found between proprioception and kinesthesia scores ($p>0.05$). However, a significant correlation was found between right and left extremity proprioception scores ($p<0.01$, $r=0.50$).

Conclusion: This study revealed the existence of proprioception and kinesthesia deficiencies in children who received chemotherapy. Planning intervention programs for these areas and evaluating sensory parameters in detail will be useful for future studies.

Keywords: Cancer, child, proprioception, kinesthesia

ÖZ

Amaç: Bu çalışmanın amacı hastanede yatan ve kemoterapi tedavisi gören farklı tanılı kanserli çocukların üst ekstremitelerinin propriosepsiyon ve kinestezi fonksiyonlarını incelemektir.

Yöntemler: Bu çalışmaya çocukluk çağı kanserli 213 (101 kadın, 112 erkek) çocuk katılmıştır. Üst ekstremitelerin propriosepsiyon ve kinestezi duyuları hastane ortamında değerlendirilmiştir. Klinik bir değerlendirme olan pozisyon hissi propriyosepsiyonu değerlendirmek için kullanılmıştır. Kinestezi duyusunu değerlendirmek için Duyu Bütünleme ve Praksis Testlerinin kinestezi alt testi kullanılmıştır. Tanı kriterlerine göre ortalama değerleri karşılaştırmak için Kruskal-Wallis testi kullanıldı. İki değişkenli korelasyonlar için Spearman korelasyon katsayısı kullanıldı ve istatistiksel anlamlılık $p<0,05$ olarak kabul edildi.

Bulgular: Tanı tiplerine göre propriosepsiyon skorları ve kinestezi ortalamaları arasında anlamlı fark yoktu ($p>0,05$). Propriosepsiyon puanlarında tanı türlerine göre en düşük puan karsinoma tanı grubunda iken en yüksek puan lenfoma tanı grubunda görülmüştür. Kinestezi açısından en fazla etkilenen lenfoma tanı grubu iken en az lösemi tanı grubu etkilenmiştir. Ayrıca propriosepsiyon ve kinestezi skorları arasında anlamlı bir ilişki bulunamamıştır ($p>0,05$). Ancak sağ ve sol ekstremite propriosepsiyon skorları arasında anlamlı bir ilişki bulunmuştur ($p<0,01$, $r=0.50$).

Sonuç: Bu çalışma kemoterapi alan çocuklarda propriosepsiyon ve kinestezi sorunlarının varlığını ortaya koymuştur. Bu alanlara yönelik müdahale programlarının planlanması ve duyusal parametrelerin detaylı olarak değerlendirilmesi ileride yapılacak çalışmalar için faydalı olacaktır.

Anahtar Sözcükler: Kanser, çocuk, propriosepsiyon, kinestezi

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Introduction

Childhood cancers are examined under 12 main groups according to the international classification of pediatric cancers. These include leukemia, nervous system tumors, lymphoma, bone tumors, neuroblastoma, Wilms' tumor and soft tissue sarcomas. Leukemia, nervous system tumors and lymphoma are the most common types (1). Detection of cancer and related treatments (eg, chemotherapy) cause undesirable physical (eg, pain, fatigue), and psychological (eg, anxiety, depression, and irritability) complications for children (2). Significant decreases occur in children's functional capacity and physical fitness compared to pre-disease period. Furthermore, multiple and sometimes prolonged hospitalizations lead to limitations and reduced quality of life of children in performing their daily activities (eg, self-care, play, social participation and educational activities) (3,4).

Sensory deficits occur in cancer due to the infestation of the nerve tissue by the tumor or the treatment received. It has been stated that the occurrence of these sensory damages in pediatric cancers may adversely affect somatosensory development (5). Proprioception, which is one of the subsystems in the somatosensory system, is defined as the awareness of the position and movement of the body and its extremities. This feeling also includes the feeling of heaviness. Proprioception allows the person to interact with the environment by regulating muscle tone, revealing voluntary movement and, giving the person the sense of where he/she is in space (6). Proprioception is generally assumed to consist of two modalities: joint position sensation (kinesthesia) and limb movement sensation. The ability to be aware of the position of body parts in space, consciously or unconsciously, defines proprioception, while kinesthesia is defined as the proprioceptive stimulation reaching the central nervous system and resulting in conscious awareness of joint position (7).

It has been shown that proprioceptive awareness is necessary to coordinate multiple joints, maintain muscle contraction, and even perform complex finger movements with vision. Functionally, individuals who have problems with the proprioceptive system have been reported to have difficulty in fine motor skills such as fastening buttons or writing (8). It has been shown that poor proprioception is associated with more activity limitations (9).

Many people diagnosed as having cancer are inevitably treated with chemotherapy despite its neurotoxic side effects (10). Since chemotherapy affects all body systems, carrying on with daily life becomes difficult for individuals. Due to the suppression of the bone marrow in the early period of the chemotherapy treatment, various side effects emerge including but not limited to leukopenia, thrombocytopenia, anemia, infection, fatigue, gastrointestinal complaints, pain, tingling, numbness, etc. (11). Studies have shown that these side effects correspond approximately to the time of the patient receiving the third cure of chemotherapy (12,13). It was observed that as the number of cures increased, the physical symptoms experienced by individuals also increased as well (14).

Correct processing of proximal sensory stimuli such as proprioception, tactile and vestibular stimuli is important in the normal neurodevelopmental period. In particular, disturbances in the somatosensory system signal processing will cause problems in postural control, movement coordination, motor development and adaptive response. These would negatively affect the child's participation in all life activities in the future (15). Assessing how a child reacts to proprioceptive signals for regulation and modulation is substantial for characterizing a child's skill to participate in activities of daily life (8).

Identified somatosensory deficits in proprioception and kinesthesia might provide clinicians for rehabilitation with information about many factors (16). It has been reported that ignoring these parameters means missing critical opportunities for interventions to enhance the children's development. Therefore, it is important to assess the child's ability to process and use proprioceptive and kinesthesia information with a comprehensive assessment (17). In many pediatric populations, such as cerebral palsy, developmental coordination disorder and children with obesity, sensory problems that negatively affect motor behavior and motor development have been reported to be associated with proprioceptive or kinesthesia deficits (18-20).

It has been shown that poor upper limb proprioception is associated with difficulties in handwriting and poor coordination (21). It has been reported that those with proprioceptive and kinesthesia deficits in the upper extremities exhibit spatially inefficient hand movements, poor spatial reference for movements, and difficulty in timing of movements (19). It has been reported in the literature that deficiencies in upper extremity proprioceptive and kinesthesia functions negatively affect quality of life and functional independence (22-24). In the light of this information little data is available on how somatosensory involvement in children with childhood cancer changes. Studies show that clinical sensory and motor changes need to be determined. This study focuses on proprioception and collectively used kinesthesia with it. The aim of the study was to examine proprioception and kinesthesia function of the upper limbs in children who were undergoing chemotherapy treatment and hospitalized with various cancer diagnoses.

Methods

The study was carried out in the inpatient clinic of the University Hospital, Department of Pediatric Oncology. Inclusion criteria for children diagnosed as having childhood cancer were as follows: (a) being between the ages of 6 and 14; (b) receiving at least three curing of chemotherapy (12); (c) not having a central or peripheral nervous system disease or disorder; (d) scoring 1.65-2.83 according to the Semmes-Weinstein Monofilament Test and scoring 7 correct answers in 10 trials for superficial pain assessment; (e) having scores higher than 28, 30 and 35 in the mini-mental state exam devised for children of ages 6-8, 9-11 and 12-14, respectively (25); and (f) not having metastases. The exclusion criteria for children were: (a) having relapsed disease or being in palliative care; (b) not speaking Turkish fluently; (c); being diagnosed as having brain tumor.

Children who received inpatient treatment during the study were included as potential participants. The sample size was calculated as a result of the power analysis performed with 80% power and 5% error rate. According to the inclusion criteria, 244 children were initially eligible. However, 31 of these children later met the exclusion criteria: Not speaking Turkish fluently enough (n=5), having relapsed disease (n=3), being diagnosed as having brain tumor (n=10), having metastases (n=7) and having a peripheral nervous system disease (n=6). Before the study procedure, an informed written consent was taken from each child and legal guardian, which was approved by the University's Ethics Committee (decision number: 677-25, date: 28.02.2017).

Assessments

In order to avoid distraction, each child was evaluated separately in their own room in a quiet environment. Demographic data (i.e. age, gender, number of cures and cancer type) were obtained during the interview. Later, proprioception and kinesthesia assessments were performed in the children. The first author evaluated kinesthesia, and the third author scored. The second author evaluated proprioception, and the last author scored. Tests were administered with dominant and non-dominant hands in an appropriate setting. Total evaluation time was approximately 15 minutes.

Proprioception (Sense of Position)

Common proprioception clinical assessments investigate the determination of the position or direction of motion in which a finger or more proximal joint passively places or moves (8). Proprioception was evaluated by evaluating the sense of motion in the elbow, wrist, thumb and index finger. The therapist moved different joints in small widths in flexion-extension and the child was instructed to say 'yes' when movement was felt. Proprioception was scored as normal (2), impaired (1), or absent (0). (2= Normal: Movement is felt in a small width with all three attempts. 1= Impaired: Movement is only felt over a greater breadth. 0= Absent: The movement is not felt in great breadth with any attempt). The test took about 5-10 minutes. The child was asked to close his/her eyes with this assessment and the therapist did not give any feedback on the accuracy of their estimates to eliminate a learning effect (17).

Kinesthesia

The kinesthesia subtest of Sensory Integration and Praxis Tests (SIPT) was used to evaluate the kinesthesia discrimination of the children under consideration. The kinesthesia test is one of 17 subtests included as part of the SIPT, developed by Ayres (26) as a standard measure of sensory integration and praxis functions in children aged 4-8 years and 11 months. The test most directly measures proprioceptive function, namely sense of movement. Therapists who have a practitioner certificate can apply this test. The child with closed eyes was asked to hold her/his fingers and move from one predetermined point to the other on the paper, and then the child was asked to repeat this movement according to her/his own sense of movement. The test took about 5 minutes. The distance to the correct point was recorded in centimeters. The mean distances of both upper limbs to the correct point were calculated. Low mean score was interpreted as good kinesthetic perception (27).

Statistical Analysis

Statistical analysis was executed by SPSS (Statistical Package for Social Sciences version 22). Data distribution normality was examined using visual and analytical methods. Outcome measurements were defined using mean and standard deviations for continuous variables and frequencies and ratios for categorical variables. Descriptive statistics were reported using medians and interquartile range for the non-normally distributed and ordinal variables. Proprioception and kinesthesia values were not normally distributed and the Kruskal-Wallis tests were conducted to compare them based on diagnosis criteria. Spearman's coefficient of correlation was used for bivariate correlations between proprioception scores and kinesthesia averages. An overall 5% type-I error level was used to infer statistical significance.

Results

Two hundred thirteen children with childhood cancer participated in this study. The demographic characteristics of the participants are shown in Table 1.

The proprioception scores of the right and left upper extremities of the participants according to the types of cancer shown in Figure 1. Proprioception scores reveal that that the carcinoma group is the most affected cancer type in the sense of proprioception.

The average of kinesthesia scores with respect to cancer types are shown in Figure 2. The lowest averages of the kinesthesia are in the leukemia group and the highest averages are in the lymphoma group. According to these results, the most affected cancer type in terms of kinesthesia sensation is lymphoma group.

The mean proprioception scores according to their cancer types is shown in Figure 3. The childhood cancers when sorted from the least affected group to the most affected group according to mean proprioception scores were lymphoma, leukemia, ewing sarcoma, osteosarcom and carcinoma.

The differences between the means of proprioception and kinesthesia according to cancer types are shown in Table 2. There were no statistically significant differences between the proprioception scores and kinesthesia averages of children with childhood cancer according to the diagnosis groups ($p>0.05$). Considering that the maximum possible proprioception score was 8, both right and left extremities average scores were low.

While standard deviations (SD) between +1 and -1 in kinesthesia scores were accepted as normal perception (27). The calculated standard deviations of kinesthesia scores were more than +1 SD among children with childhood cancer. Therefore, it was observed that the kinesthetic perceptions of children were negatively affected with cancer.

The relationship between right and left extremity proprioception scores and means of kinesthesia values are shown in Table 3. A

significant moderate positive correlation was found between right and left extremity proprioception scores (RSpearman=0.50, p<0.01). No correlations were detected proprioception scores between with mean of kinesthesia scores (p>0.05).

Discussion

The aim of this study was to examine proprioception and kinesthesia functions of the upper limbs in children with childhood cancer undergoing chemotherapy treatment who were hospitalized according to different diagnosis groups. It was observed that the average proprioception levels of children with childhood cancer were low. The carcinoma group showed the lowest, while the lymphoma group showed the highest proprioception scores among various types of cancer. In terms of kinesthesia scores, the lymphoma group was the most affected types of cancer. Also, no difference was detected in proprioception (both right and left limb) and kinesthesia values according to cancer types. In addition to these, a significant relationship between right and left proprioception values was found. However, there was no relationship between kinesthesia and proprioception values.

Table 1. The demographic characteristics of childhood cancer with children

Mean ± SD n=213	
Age (year)	11.16±3.03
Number of cures	3.73±0.73
Type of cancer	n (%)
Osteosarcoma	46 (21.6)
Ewing sarcoma	54 (25.4)
Lymphoma	37 (17.4)
Leukemia	37 (17.4)
Carcinoma	39 (18.3)
Gender	
Female	101 (47.4)
Male	112 (52.6)
Dominant hand	
Right	137 (64.3)
Left	76 (35.7)
SD: Standard deviation	

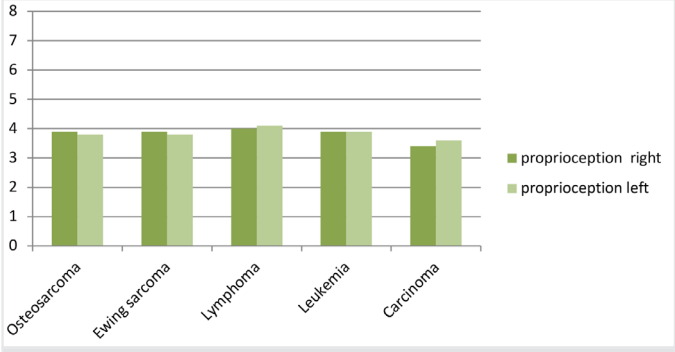

Figure 1. Proprioception scores according to types of childhood cancer

It is emphasized that a sedentary lifestyle accelerates the loss of proprioceptive acuity (6). Wang et al. (20) examined the proprioception of knee and ankle joints in pre-pubertal obese and non-obese boys. The study concluded that obese boys showed deficit proprioception in knee flexion (20). In another study evaluating the proprioception of children with cerebral palsy, proprioceptive deficit was found in all limbs of children (16). Most childhood cancers are more common in boys, and this is even more evident in developing countries (28). In the light of this information, the high number of boys in our study is similar to the literature. Considering that we had a higher number of boys in our study, it was not surprising that their proprioception levels were low. Cancer treatment usually requires repeated and/or prolonged hospitalization (29). It has been stated that in children with cancer who are hospitalized for a long time, the opportunity to establish an active relationship with environment decreases and the ability to process and use sensory information to organize, direct and regulate behavior in the future is negatively affected (30). The results of our study showed that considering the maximum possible score in proprioception was 8, the scores of children with childhood cancer were quite low. We claim that this is because the treatment of cancer in childhood takes months and children often stay in hospitals for a long time. According to the results in our study, the lowest proprioception scores belong to the carcinoma group. Our study demonstrated that although the evaluation of the sense of proprioception was very important in all cancer types, children with carcinoma who had the lowest proprioception scores should especially be focused on during related evaluations and interventions.

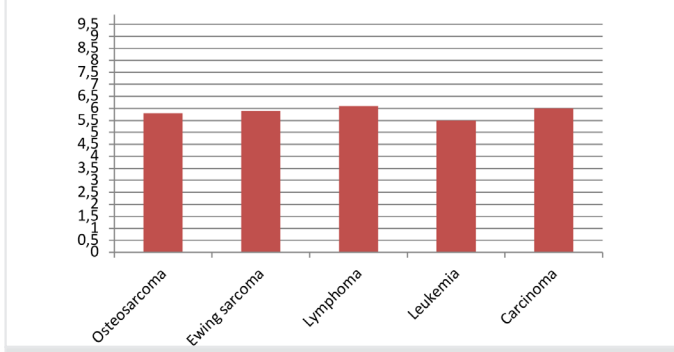

Figure 2. Averages of kinesthesia considering types of childhood cancer

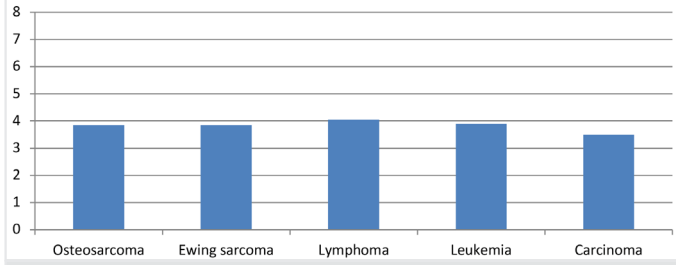

Figure 3. The mean of proprioception scores considering types of childhood cancer

A study conducted to measure and compare kinesthetic sensitivity in children who were typically developing and in children with Developmental Coordination Disorders (DCD) showed that children with DCD were significantly less sensitive to the sense of kinesthesia (18). In another study examining the kinesthesia sense of children with specific language disorders, it was reported that these children performed poorly in kinesthesia tasks (31). In our study, it was found that the distance of the average of the kinesthesia scores to the target point was quite high. Hence, we can state that the kinesthesia senses are also affected in children with cancer. In a study conducted on the writing analysis of children receiving leukemia treatment, it was stated that children could overcome problems other than the constantly increasing drawing pressure and this increased drawing pressure might be related to the children's attempt to obtain sufficient kinesthetic information (32). In a study of fine motor and tactile-perceptual functions in children with cancer, they found transient problems in children treated for leukemia and more persistent problems in children treated for solid tumors (33). It was stated that children who experienced the side effects of cancer treatment or who were hospitalized for a long time due to illness had difficulty in learning and participating in play activities and therefore lost opportunities to improve in their physical, problem-solving and social-interactive skills (34). Based on the findings in the literature, we think that children with cancer will experience more problems in their playing, fine motor skills, academic performance and social relationship skills if their sensory deficiencies are left unidentified and untreated. According to our study, it was shown that the leukemia group was better than other diagnostic groups in terms of kinesthesia, and the lymphoma group was the most affected of childhood cancer types. For this reason, it would especially be useful to evaluate children with lymphoma in the early period and to plan interventions in this area.

Table 2. The differences between the means of proprioception and kinesthesia according to cancer types

Variable	Cancer types	Mean ± SD	p
Proprioception right (0-8)	Osteosarcoma	3.97±1.08	0.10
	Ewing sarcoma	3.98±0.99	
	Lymphoma	4.05±1.02	
	Leukemia	3.94±1.02	
	Carcinoma	3.48±0.75	
Proprioception left (0-8)	Osteosarcoma	3.86±0.95	0.44
	Ewing sarcoma	3.81±0.93	
	Lymphoma	4.10±0.87	
	Leukemia	3.94±0.88	
	Carcinoma	3.74±0.78	
Kinesthesia (cm)	Osteosarcoma	5.89±1.39	0.79
	Ewing sarcoma	5.94±1.20	
	Lymphoma	6.19±1.06	
	Leukemia	5.51±0.90	
	Carcinoma	6.06±0.98	

SD: Standard deviation, min: Minimum; max: Maximum. The significance of differences for means of the proprioception and kinesthesia was compared using the Kruskal-Wallis test.
P-values of <0.05 were considered significant

Table 3. Correlation between the proprioception scores and kinesthesia

Variable	n	Mean ± SD	1.	2.	3.
1. Proprioception right	213	3.90±1.08	-	0.001*	0.28
2. Proprioception left	213	3.69±0.92		-	0.15
3. Kinesthesia	213	5.92±1.15			-

SD: Standard deviation; min: Minimum; max: Maximum. P-values of <0.05 were considered significant *p<0.001

Childhood cancers vary according to the type of the disease, the organ in which it is located, and the individual characteristics of the patient (35). Carcinoma is the name given to the tumoral mass that occurs in the skin or in the epithelial cells surrounding the internal organs (36). The skin, muscles, and joints of limbs are richly innervated by a variety of sensory receptors that convey proprioceptive information to all levels of the nervous system. It is known that loss or impairment of sensation in the limbs can lead to serious movement disorders and sensory input plays a critical role in controlling movement (37). Carcinoma tumors can also arise in cutaneous cells that are associated with proprioception (38). In the results of our study, it was revealed that the carcinoma group was more affected in the proprioceptive area, which was in line with this information in the literature. Lymphomas are malignant diseases originating from lymphoreticular cells. These types of cells are found mainly in the lymph nodes, and the leading clinical symptom is tumoral enlargement of the lymph nodes (39). Lymphedema can be seen as a secondary symptom in lymphoma (40). It has been reported in the literature that loss of kinesthetic sensation is associated with upper extremity lymphedema (41,42). In the results of our study, it was seen that the lymphoma group was most affected in the sense of kinesthesia. However, we think that it will be valuable to reveal whether this condition is associated with lymphedema in future studies.

Proprioception contributes to body image, and the development of motor control when learning new skills (43). Chancel et al. (44), emphasized that proprioceptive afferents were bilaterally integrated during bimanual tasks. Several studies have highlighted strong interactions between the muscle proprioceptive afferents for the two arms (45,46). In our study, a moderately significant correlation was found between right and left proprioception scores. Our finding is in line with the results in the literature. According to our results, we can state that approaches involving the coordination of extremities and bilateral activities are needed in children with childhood cancer due to low proprioception mean scores and a significant relationship between the two extremities.

Study Limitations

There were some limitations to this study. Primarily, these findings could not be generalized for age and childhood cancer types not included in our study, depending on the heterogeneous population. Secondly, there was no control group of same aged

healthy children. Another limitation of our study was that we only evaluated the upper extremity and not the lower extremity in our study.

Conclusion

This study provides valuable information on the proprioception and kinesthesia senses of children with childhood cancer, an area which has not yet been explored adequately in an early phase of pediatric oncological aftercare. Early identification of sensory impairment is especially relevant in pediatric populations as sensory dysfunction is occurring during somatosensory development (47). The studies in the literature conducted in children with similar chronic or neurological diseases show that sensory impairments closely affect the development of motor skills. Thus, considering our study results, we think that sensory deficits may also affect motor skills in children with cancer. Sensory problems can potentially be critical, as proprioceptive transmitters are required for strong motor behaviors such as fine motor skills and balance. In this respect, it will be important to include sensorimotor interventions, which are an important component of long-term care, in the treatment protocol, together with early detection of proprioception and kinesthesia deficits in children with childhood cancer. Sensory assessments may also be useful for identifying and monitoring other patient populations with known or potential sensory dysfunction, such as other pediatric cancers and individuals with adult cancers. Further investigation and analysis of sensory skills of children with cancer are recommended.

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Ethics

Ethics Committee Approval: Before the study procedure, an informed written consent was taken from each child and legal guardian, which was approved by the University's Ethics Committee (decision number: 677-25, date: 28.02.2017).

Informed Consent: Before the study procedure, an informed written consent was taken from each child and legal guardian.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.H., Design: S.Ş., Data Collection or Processing: Z.K., C.D., Analysis or Interpretation: M.H., S.Ş., Literature Search: Z.K., C.D., writing: Z.K., C.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. American Academy of Pediatrics Section on Hematology/Oncology Children's Oncology Group. Long-term follow-up care for pediatric cancer survivors. Pediatrics 2009;123:906-15.
2. Stubblefield MD. Cancer rehabilitation: principles and practice: Springer Publishing Company; 2018.
3. Mohammadi A, Mehraban A. Play-based occupational therapy for hospitalized children with cancer: A short communication. Iran Rehabil J 2020;18:17-22.
4. Rankin J, Murtagh N, Robb K, Cooper J, Lewis S. Rehabilitation in cancer care: John Wiley & Sons; 2009.
5. Moore RJ, Groninger H. Chemotherapy-induced peripheral neuropathy in pediatric cancer patients. Cureus 2013;5:e124.
6. Suetterlin KJ, Sayer AA. Proprioception: where are we now? A commentary on clinical assessment, changes across the life course, functional implications and future interventions. Age Ageing 2014;43:313-8.
7. Mourcou Q, Fleury A, Diot B, Franco C, Vuillerme N. Mobile phone-based joint angle measurement for functional assessment and rehabilitation of proprioception. Biomed Res Int 2015;2015:328142.
8. Findlater SE, Dukelow SP. Upper extremity proprioception after stroke: bridging the gap between neuroscience and rehabilitation. J Mot Behav 2017;49:27-34.
9. Scheper M, Rombaut L, de Vries J, De Wandele I, van der Esch M, Visser B, et al. The association between muscle strength and activity limitations in patients with the hypermobility type of Ehlers–Danlos syndrome: the impact of proprioception. Disabil Rehabil 2017;39:1391-7.
10. Neil EC, Hanmantgad S, Khakoo Y. Neurological complications of pediatric cancer. J Child Neurol 2016;31:1412-20.
11. Monfort SM, Pan X, Loprinzi CL, Lustberg MB, Chaudhari AM. Impaired postural control and altered sensory organization during quiet stance following neurotoxic chemotherapy: a preliminary study. Integr Cancer Ther 2019;18:1534735419828823.
12. Beser N. Öz F. Kemoterapi alan lenfomalı hastaların anksiyete-depresyon düzeyleri ve yaşam kalitesi, CÜ Hemşirelik Yüksekokulu Dergisi. 2003;7:47-58.
13. Norum J, Wist EA. Quality of Life in Survivors of Hogkins' Disease. Qual Life Res 1996;5:257-67.
14. Yeşilbalkan ÖU, Akyol AD, Çetinkaya Y, Altın T, Deniz Ü. Studying the Symptoms that are Being Experienced due to Treatment by the Patients who Receive Chemotheraphy and Their Effects on the Quality of Life. Ege Üniversitesi Hemşirelik Yüksek Okulu Dergisi. 2005;21:13-31.
15. Gardner E, Johnson K. The somatosensory system: receptors and central pathways. Principles of neural science. 2013;5:475-95.
16. Wingert JR, Burton H, Sinclair RJ, Brunstrom JE, Damiano DL. Joint-position sense and kinesthesia in cerebral palsy. Arch Phys Med Rehabil 2009;90:447-53.
17. Chu VWT. Assessing proprioception in children: A review. J Mot Behav 2017;49:458-66.
18. Li KY, Su WJ, Fu HW, Pickett KA. Kinesthetic deficit in children with developmental coordination disorder. Res Dev Disabil. 2015 Mar;38:125-33.
19. Goble DJ, Lewis CA, Hurvitz EA, Brown SH. Development of upper limb proprioceptive accuracy in children and adolescents. Hum Mov Sci 2005;24:155-70.
20. Wang L, Li JX, Xu DQ, Hong YL. Proprioception of ankle and knee joints in obese boys and nonobese boys. Med Sci Monit 2008;14:CR129-CR35.

21. Falk TH, Tam C, Schwellnus H, Chau T. Grip force variability and its effects on children's handwriting legibility, form, and strokes. J Biomech Eng 2010;132:114504.
22. Ribeiro F, Oliveira J. Aging effects on joint proprioception: the role of physical activity in proprioception preservation. Eur Rev Aging Phys Act 2007;4:71-6.
23. Hughes CML, Tommasino P, Budhota A, Campolo D. Upper extremity proprioception in healthy aging and stroke populations, and the effects of therapist-and robot-based rehabilitation therapies on proprioceptive function. Front Hum Neurosci 2015;9:120.
24. Adamo DE, Martin BJ, Brown SH. Age-related differences in upper limb proprioceptive acuity. Percept Mot Skills 2007;104:1297-309.
25. Jain M, Passi G. Assessment of a modified Mini-Mental Scale for cognitive functions in children. Indian Pediatr 2005;42:907-12.
26. Ayres AJ. Sensory integration and praxis tests (SIPT): Western Psychological Services (WPS) Los Angeles, CA; 1996.
27. Van Jaarsveld A, Mailloux Z, Herzberg DS. The use of the Sensory Integration and Praxis tests with South African children. S Afr J Occup Ther. 2012;42(3):12-8.
28. Parkin D, Kramarova E, Draper G, Masuyer E, Michaelis J, Neglia J, et al. International incidence of childhood cancer(Volume II). IARC scientific publications. 1998.
29. Speyer E, Herbinet A, Vuillemin A, Briançon S, Chastagner P. Effect of adapted physical activity sessions in the hospital on health-related quality of life for children with cancer: A cross-over randomized trial. Pediatr Blood Cancer 2010;55:1160-6.
30. Lin SH, Cermak S, Coster WJ, Miller L. The relation between length of institutionalization and sensory integration in children adopted from Eastern Europe. Am J Occup Ther 2005;59:139-47.
31. Marton K. Imitation of body postures and hand movements in children with specific language impairment. J Exp Child Psychol 2009;102:1-13
32. Reinders-Messelink H, Schoemaker M, Snijders T, Göeken L, Bökkerink J, Kamps W. Analysis of handwriting of children during treatment for acute lymphoblastic leukemia. Med Pediatr Oncol: The Official Journal of SIOP—International Society of Pediatric Oncology (Societé Internationale d'Oncologie Pédiatrique. 2001;37(4):393-9. https://doi.org/10.1002/mpo.1216
33. Dodzik PA, Fulton R. Neuropsychological outcomes in children with acute lymphoblastic leukemia. In: Mucci GA, Torno LR, editors. Handbook of Long Term Care of The Childhood Cancer Survivor Specialty Topics in Pediatric Neuropsychology. Boston, MA: Springer; 2015. p. 223-47.
34. Keene N. Childhood leukemia: A guide for families, friends & caregivers: Childhood Cancer Guides. United States of America, O'Reilly Media, 2010.
35. Bowen JM, Wardill HR. Advances in the understanding and management of mucositis during stem cell transplantation. Curr Opin Support Palliat Care 2017;11:341-6.
36. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
37. van der Wal J. The architecture of the connective tissue in the musculoskeletal system—an often overlooked functional parameter as to proprioception in the locomotor apparatus. Int J Ther Massage Bodyw 2009;2:9-23.
38. Gleason JM, Köhler TS, Monga M. Merkel cell carcinoma metastatic to testis. Urology. 2006;67:423-e13- 14.
39. Du J, Zhang Y. Sequential anti-CD19, 22, and 20 autologous chimeric antigen receptor T-cell (CAR-T) treatments of a child with relapsed refractory Burkitt lymphoma: a case report and literature review. J Cancer Res Clin Oncol 2020;146:1575-82.
40. Rymal C. Lymphedema management in patients with lymphoma. Nurs Clin North Am 2001;36:709-34.
41. Hwang R, Kentish M, Burns Y. Hand positioning sense in children with spina bifida myelomeningocele. Aust J Physiother 2002;48:17-22.
42. Karadibak D, Yavuzsen T. Evaluation of kinesthetic sense and hand function in women with breast cancer-related lymphedema. J Phys Ther Sci 2015;27:1671-5.
43. Stillman BC. Making sense of proprioception: the meaning of proprioception, kinaesthesia and related terms. Physiotherapy 2002;88:667-76.
44. Chancel M, Kavounoudias A, Guerraz M. What's left of the mirror illusion when the mirror can no longer be seen? Bilateral integration of proprioceptive afferents! Neuroscience 2017;362:118-26.
45. Brun C, Guerraz M. Anchoring the "floating arm": use of proprioceptive and mirror visual feedback from one arm to control involuntary displacement of the other arm. J Neurosci 2015;310:268-78.
46. Kuehn E, De Havas J, Silkoset E, Gomi H, Haggard P. On the bimanual integration of proprioceptive information. Exp Brain Res 2015;233:1273-88.
47. Holst-Wolf JM, Yeh I, Konczak J. Development of proprioceptive acuity in typically developing children: normative data on forearm position sense. Front Hum Neurosci 2016;10:436.

Original Article

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Comparison of Glasgow Blatchford and New Risk Scores to Predict Outcomes in Patients with Acute Upper GI Bleeding

Akut Üst GIS Kanaması Olan Hastalarda Sonuçları Öngörmede Glasgow Blatchford ve Yeni Risk Skorlarının Karşılaştırılması

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ABSTRACT

Objective: Upper gastrointestinal (GI) bleeding constitutes a significant number of admissions to the emergency department, and it has high rates of morbidity and mortality. In this study, the contribution of new scores, such as The International Bleeding Risk Score (ABC score) and the Horibe GI bleeding prediction score (HARBINGER), to clinical practice was investigated. Using scores that are easy to calculate and memorable when used in the emergency department enables a more efficient use of medical resources. In addition, it may contribute to solving the problems regarding determining the need for intensive care in patients with upper GI bleeding.

Methods: This study was conducted retrospectively on patients over the age of 18 who were admitted to the emergency department between September 1, 2018 and August 31, 2019. The HARBINGER and ABC scores and the Glasgow Blatchford score (GBS) were calculated for each patient. Following that, the need for intensive care, mortality, re-bleeding rate, and transfusion need were compared.

Results: This study included 184 patients. When predicting the need for intensive care, the ABC score had a higher AUC value than the GBS and HARBINGER score, even when there was a low cut-off value (cut-off value >4). (AUC =0.944, specificity =0.74, sensitivity =0.83).

Conclusion: This study found that the ABC score could be used to predict the need for intensive care in upper GI bleeding, and

ÖZ

Amaç: Üst gastrointestinal (Gİ) kanaması acil servise başvuruların önemli bir kısmını oluşturur. Yüksek oranda morbidite ve mortaliteye sahiptir. Bu hastaların prognoz tahmini için birçok skor kullanılmaktadır. Bu skorların çoğu düşük riskli hastalar için kullanışlı görünmektedir ve yoğun bakım tahmini konusunda performanları zayıf bulunmuştur. Bu çalışmada ABC ve HARBINGER gibi yeni skorların klinik pratiğe olan katkısı araştırılmıştır. Acil serviste kolay hesaplanan ve akılda kalıcı bu skorları kullanmak tıbbi kaynakların daha verimli kullanımına olanak tanır. Ayrıca üst Gİ kanamalı hastalarda yoğun bakım ihtiyacının belirlenmesinde yaşanan sorunların çözümüne katkı sağlayabilir.

Yöntem: Bu çalışma 1 Eylül 2018 ile 31 Ağustos 2019 tarihleri arasında acil servise başvuran 18 yaş üstü hastalar üzerinden geriye dönük olarak yapıldı. Her hasta için HARBINGER ve ABC skorları ile Glasgow Blatchford skoru (GBS) hesaplandı. Ardından yoğun bakım ihtiyacı, mortalite, tekrar kanama ve transfüzyon ihtiyacı karşılaştırıldı.

Bulgular: Bu çalışmaya 184 hasta dahil edildi. Yoğun bakım ihtiyacı konusunda kesme değeri düşük olmasına rağmen (cut-off değeri >4) ABC skoru GBS ve HARBINGER skorundan daha yüksek bir AUC değerine sahipti. (AUC =0,944, özgüllük =0,74, duyarlılık =0,83).

Sonuç: Bu çalışma ile ABC skorunun üst GİS kanamalarında yoğun bakım ihtiyacını öngörmede kullanılabileceğini ve diğer skorlara göre daha iyi performans gösterdiğini bulduk. Ayrıca parametreleri

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that it outperformed other scores. Additionally, we concluded that the HARBINGER score, which had a "shock index" among its parameters, was not effective in predicting in-hospital adverse events.

Keywords: ABC score, HARBİNGER, Glasgow Blatchford score, intensive care

arasında "şok indeksi" bulunan HARBINGER skorunun hastane içi advers olayları öngörmede etkili olmadığı sonucuna vardık.

Anahtar Sözcükler: ABC skoru, HARBİNGER, Glasgow Blatchford skoru, yoğun bakım

Introduction

Upper gastrointestinal (GI) bleeding constitutes a significant number of admissions to the emergency department, and it has high rates of morbidity and mortality. Despite recent improvements regarding its management, the mortality rate remains at approximately 10% (1). Its estimated incidence is around 67-103/100,000 per year (1,2). Patients may present with chronic anemia because of the occult bleeding or hypovolemic shock due to the excessive bleeding (3). Therefore, the patients that need to be prioritized for emergency treatment must be determined. As the current guidelines recommend the use of prognostic risk scores in the management of upper GI bleeding (4), many risk scores have been developed. The most common scores include the Rockall score and the Glasgow Blatchford score (GBS). Although these scores have many positive aspects, their effectiveness is limited, especially in intensive care estimations. Moreover, many parameters must be calculated, and this is not memorable. For this reason, they are not used routinely in emergency services. It is important to use non-invasive, low-cost scores that can be evaluated alongside routine blood parameters to predict the bleeding severity and prognosis in non-varicose upper GI bleeding (5).

The Horibe GI bleeding prediction score (HARBINGER) has been recently developed, which is a simple score that can be easily calculated. This score comprises the following three parameters: not using proton pump inhibitors (PPIs) in the week before admission; the shock index and blood urea nitrogen/creatinine of <30. Although the ABC score has been recently developed, studies have shown that it performs better than the other scores in predicting mortality. In the ABC score, the age, blood test, and comorbidities of the patients are evaluated (Table 1) (6,7).

Although many risk scores have been developed regarding the evaluation of patients with GI bleeding, there is no widely accepted risk score in clinical practice. In this study, the contribution of new scores, such as ABC and HARBINGER, to clinical practice will be evaluated. Using scores that are easily calculated and memorable when used in the emergency department enables a more efficient use of medical resources. In addition, it may contribute to solving the problems regarding determining the need for intensive care in patients with upper GI bleeding.

Methods

This study was conducted retrospectively between September 1, 2018 and August 31, 2019 on patients over the age of 18 who were admitted to the emergency department. Information about the patients was obtained from emergency service forms and hospital records. The data were analyzed using the International Classification of Diseases-10 diagnostic codes. Patients with varicose bleeding, those who did not undergo an endoscopy, those who did not have upper GI bleeding revealed in an endoscopy, trauma patients, and patients with incomplete data were excluded from the study (Figure 1).

The patients' age, gender, chronic diseases, admission complaints, drug use (oral or intravenous PPI), symptoms (hematochezia, hematemesis, melena, syncope), vital findings, level of consciousness, rectal examination findings, laboratory results (renal function, coagulation, hemoglobin, hematocrit, thrombocyte, albumin), endoscopy findings, blood transfusion, re-bleeding incidence, duration of hospital stay, and outcomes were recorded.

The HARBINGER and ABC scores and the GBS were calculated separately for each patient. The score ranges were 0-3 points for the HARBINGER score, 0-18 points for the ABC score, and 0-29 points for the GBS. Hemodynamic instability that developed in the patients' follow-ups was accepted as re-bleeding. The transfusion need, re-bleeding, mortality, and intensive care follow-up were regarded as in-hospital adverse events. The receiver operator characteristics (ROC) curve analysis was used to find the cut-off values of the categorical variables based on numerical values.

Outcomes

The primary outcome was to predict the need for intensive care in patients with upper GI bleeding, as confirmed by an endoscopy. The secondary outcomes were to evaluate in-hospital adverse events, such as mortality, re-bleeding, and the need for blood transfusion.

Determination of Variables

The patients' clinical history, use of PPIs, and laboratory tests were evaluated, and their vital signs, shock index (heart rate, systolic blood pressure), and whether there was an altered mental state were documented.

Statistical Analysis

The behaviors of the quantitative variables were expressed using centralization and variance measures with the mean ± standard deviation. To show the behavioral differences between the group mean values, the ANOVA t-test was used when the normality and uniformity assumptions were met, and the Mann-Whitney U test (number of groups =2), which was a non-parametric method, was used for the remaining cases. The diagnostic performance of the parameters was assessed using an ROC analysis. A statistical significance was accepted when the two-sided p-value was lower than 0.05. The statistical analysis was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). The area under the ROC curves (AUROCs) was calculated using 95% confidence intervals and compared based on the method described by Delong et al.

Missing Data

The prevalence and patterns of the missing data were evaluated and found to be randomly missing (Little's test: p=0.085>0.05). The missing data in the main cohort was handled by excluding these patients, who comprised 39% of the overall sample.

Ethical Approval

The approval with the number 2021/170 and date April 27, 2021 was obtained from the University Ethics Committee to allow the study to be conducted.

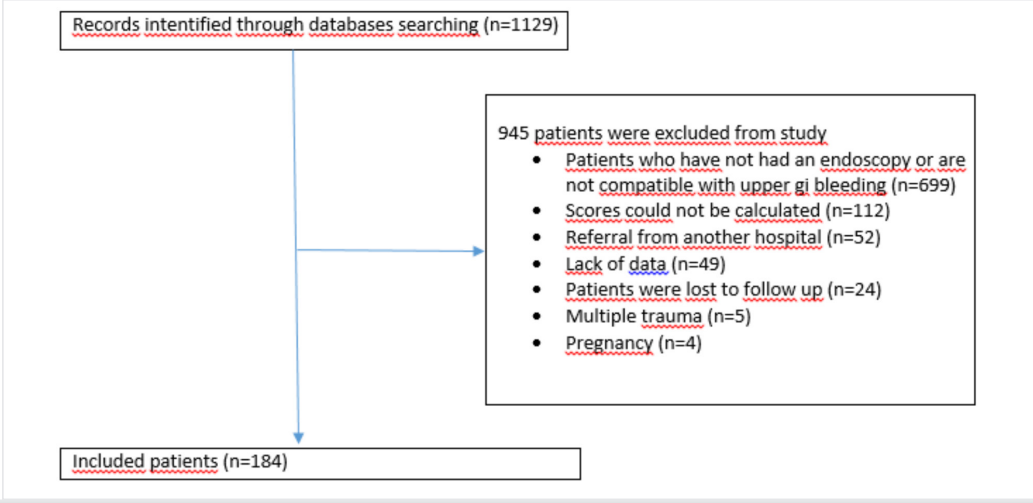

Figure 1. Flowchart of patient selection

Table 1. Characteristics of scoring systems

ABC score		GBS		HARBINGER	
Parameters	Point	Parameters	Point	Parameters	Point
Age Years	1 (60-74) 2 (>75)	Systolic BP mmHg	1 (100-109) 2 (90-99) 3 (<90)	Shock index	1 (≥1)
Urea mmol/L	1 (>10)	Urea mmol/L	2 (6.5-8) 3 (8-10) 4 (10-25) 6 (>25)	Urea/creatinine	1 (≥140)
Creatinine µmol/L	1 (100-150) 2 (>150)	Hemoglobin gr/dL	1 (12-12.9) 3 (10-11.9) 6 (<10)	PPI use (in a week)	1
Albumin	1 (<30 g/L)	Heart rate	1 (≥100)		
Mental status	2 (altered)	Syncope	2		
Cirrhosis	2	Hepatic disease	2		
Malignancy	4	Melena	1		
ASA	1 (score 1-3) 3 (score ≥4)	Cardiac failure	2		

ABC: The International Bleeding Risk Score, ASA: American Society of Anesthesiologists score, GBS: Glasgow-Blatchford score, HARBINGER: Horibe GI bleeding prediction score, Shock index: Heart rate/systolic blood pressure, PPI: Proton pump inhibitör

Results

Of the 184 patients included in the study, 61.4% were men (n=113), 38.6% were women (n=71), and the general mean age was 62.4±18.8 (21-91) years. The mean ages of the men and women were 58.3±17.8 years and 69.1±14.6 years, respectively (p=0.02). The patients' complaints at admission included dyspepsia and heartburn (n=80, 43.5%), abdominal pain (n=47, 25.5%), nausea/vomiting (n=45, 24.5%), dizziness (n=6, 3.3%), and syncope (n=6, 3.3%). The bleeding types were melena (n=132, 71.7%), hematemesis (n=29, 15.8%), hematothesis (n=18, 9.8%), and active bleeding and other (n=5, 2.7%). Out of the patients, 135 (73.4%) had no history of bleeding, and 61 patients (33.2%) were not using any medication. Forty-one (22.3%) patients were taking antiplatelet agents, 23 (12.5%) anticoagulants, 15 (8.2%) new generation anticoagulants, 10 (5.4%) non-steroidal anti-inflammatory drugs, and 34 other drugs (18.5%).

The chronic diseases of the patients were as follows: hypertension (n=76, 41.3%), diabetes mellitus (n=49, 26.6%), coronary artery disease (n=41, 22.3%), heart failure (n=21, 11.4%), renal disease (n=16, 8.7%), liver disease (n=16, 8.7%), malignancy (n=13, 7.1%), and cerebrovascular events (n=10, 5.4%). A change in consciousness was not detected in 166 of the patients (95.7%). The vital parameters and laboratory results of the patients at the time of admission are given in Table 2. The hemoglobin level was 9.26+1.88 g/dL, the hematocrit was 28.7%+5.76, and the mean corpuscular volume was 82.2+8.02 fL. Albumin levels were 2.35±0.489 g/dL in 21 patients during the intensive care follow-up, 3.42±0.597 g/dL in 163 patients outside the intensive care follow-up, and 3.31±0.675 g/dL in a total of 184 patients (Table 3). The rectal examination findings of the patients showed melena or hematochezia in 124 patients (67.4%). The number of patients who required transfusion was 98 (53.3%), and 15

Table 2. Vital signs and score averages

	Units	Mean ± SD	Median (IQR25-75)
Systolic blood pressure	mmHg	110.5±14.8	110 (100-115)
Diastolic blood pressure	mmHg	64.03±12.1	65 (56-73)
Respiratory rate	/min	10.4±9.6	18 (0-20)
Heart rate	Bpm	93.9±19.2	91 (80-107)
Hospitalization	Hour	103.2±136.7	72 (24-72)
Blood transfusion	Number	1.4±1.8	1 (0-2)
ABC	Score	3.8±2.5	3 (2-5)
GBS	Score	7.9±4.4	8 (4-11)
HARBINGER	Score	1.5±0.7	1 (1-2)

ABC: The International Bleeding Risk Score, GBS: Glasgow-Blatchford score, HARBINGER: Horibe GI bleeding prediction score

Table 3. Clinical characteristics and laboratory values of the study patients

	Units	Number (n)	Percent number (% n)
Sex	Male	113	61.4
	Female	71	38.6
		Mean ± SD	Median (IQR25-75)
Age	Years	62.4+18.8	66.5 (51-76)
WBC	10^3/µL	8.92+3.5	8.6 (6.12-11)
BUN	mg/dL	29.1+21.3	24.5 (17-32)
BUN/Cre	%	29+11.7	25 (19.2-36)
Creatinine	mg/dL	1.1+0.8	0.9 (0.7-1.5)
Prothrombin time	Sec.	15.7+2.2	15.2 (14.8-16.1)
INR	Ratio	1.7+2.2	1.2 (1.1-1.36)
LDH	U/L	202+68.7	184 (155-234.5)
Sodium	mmol/L	137.7+3.04	138 (155-234.5)
Potassium	mmol/L	4.17+0.4	4.1 (3.9-4.3)
Hemoglobin	g/dL	9.2+1.8	9.2 (8.2-10)
Hematocrit	%	28.7+5.7	29 (25.5-32.6)
MCV	fL	82.2+8	29 (25.5-32.6)
Platelet	10^3/µL	256.3+99.8	247 (204-305.5)
Albumin	g/dL	3.3+0.6	3.3 (2.9-3.8)

WBC: White blood cell, LDH: Lactate dehydrogenase, BCR: Blood urea nitrogen/creatinine ratio, INR: International Normalized Ratio, MCV: Mean corpuscular volüme, BUN: Blood urea nitrogen

patients had re-bleeding (8.2%). Eight people died in total, and the in-hospital mortality rate was 4.3%. The number of patients who were placed into intensive care was 21 (11.4%), and the total number of patients who were hospitalized was 148 (80.4%).

The mean ABC score was 3.8±2.5 (2-5), the mean GBS was 7.9±4.4 (4-11), and the mean HARBINGER score was 1.5±0.7 (1-2) (Table 3). The intensive care statistics for the scores are as follows: the ABC score (AUC =0.944, cut-off value >4, specificity (Spe) =0.74, sensitivity (Sen) =0.83), the GBS (AUC =0.789, cut-off value >11, Spe =0.82, Sen =0.66), and the HARBINGER score (AUC =0.511, cut-off value ≤2, Spe =0.11, Sen =0.95) (Figure 2). The mortality statistics for the scores are as follows: the ABC score (AUC =0.951, cut-off value >5, Spe =0.79, Sen =0.100), the GBS (AUC =0.781, cut-off value >12, Spe =0.87, Sen =0.75), and the HARBINGER score (AUC =0.633, cut-off >1, Spe =0.52, Sen =0.75) (Figure 3). The median value of the scores, AUC, cut-off value, and the Spe and Sen values in terms of the need for transfusion and re-bleeding are shown in Figures 4 and 5 (Table 4).

Discussion

This study found that the ABC score could be used to predict the need for intensive care in upper GI bleeding, and it outperformed other scores. The scores that are used in upper GI bleeding are generally used to identify low-risk patients. However, there is a need to develop tools that can correctly classify high-risk patients because the clinical evaluation process for potential high-risk patients is important. In previous studies, this process was managed by "good care overall" in only 44% of the patients. The first approach toward patient management is to evaluate the severity of the bleeding. Systemic arterial hypotension often develops in patients with severe bleeding, especially in massive bleeding, in which 20-25% of the intravascular volume is lost and the patient goes into hypovolemic shock (8,9). One of the most common causes of hypovolemic shock is GI bleeding (10). The use of the shock index (heart rate/systolic blood pressure) could be considered a predictor of hypovolemia in predicting the prognosis of these patients because the shock index is a sensitive blood loss

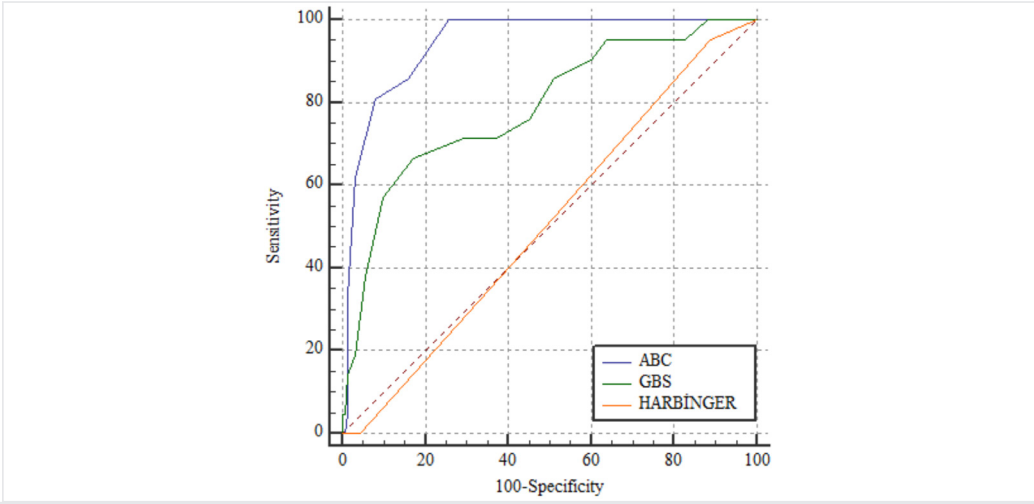

Figure 2. Prediction of intensive care

ABC: The International Bleeding Risk Score, GBS: Glasgow-Blatchford score, HARBINGER: Horibe GI bleeding prediction score

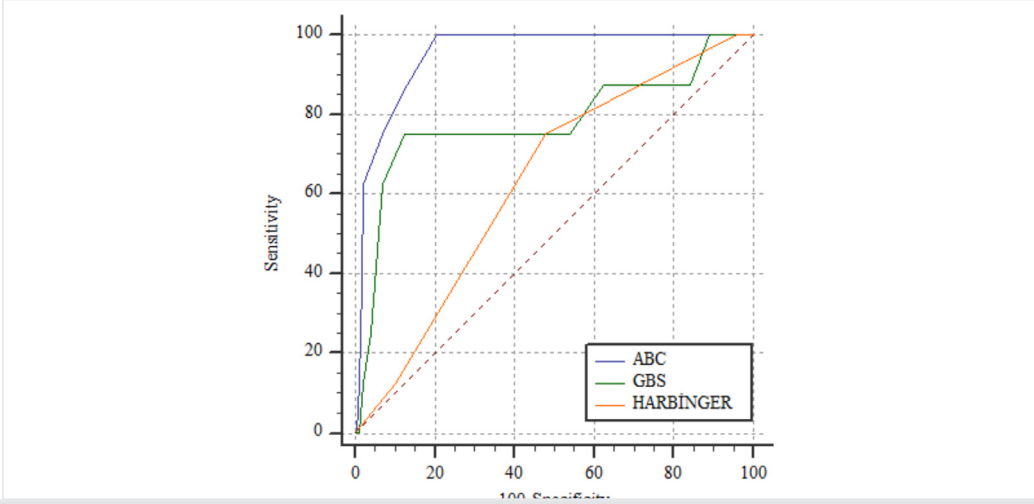

Figure 3. Prediction of mortality

ABC: The International Bleeding Risk Score, GBS: Glasgow-Blatchford score, HARBINGER: Horibe GI bleeding prediction score

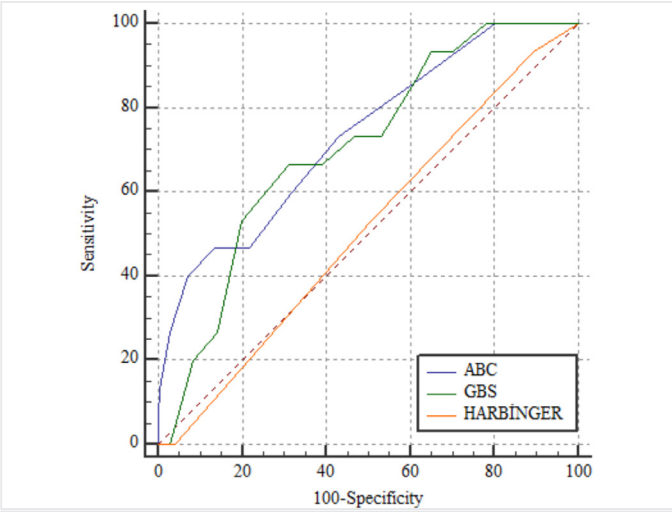

Figure 4. Prediction of re-bleeding

ABC: The International Bleeding Risk Score, GBS: Glasgow-Blatchford score, HARBINGER: Horibe GI bleeding prediction score

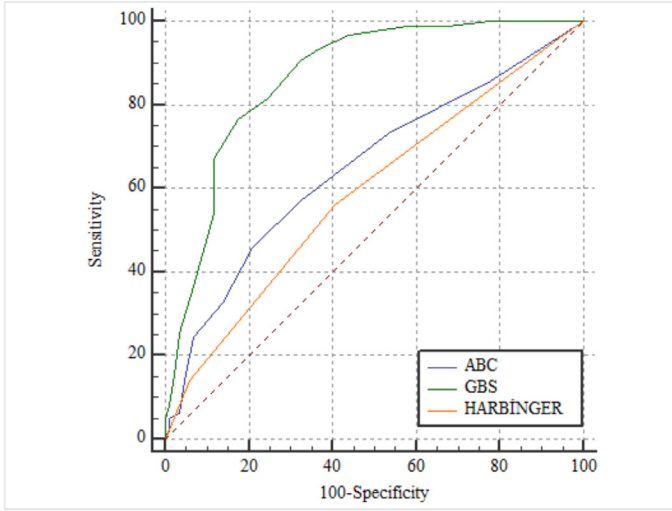

Figure 5. Prediction of need for transfusion

ABC: The International Bleeding Risk Score, GBS: Glasgow-Blatchford score, HARBINGER: Horibe GI bleeding prediction score

Table 4. ROC values of all risk scores for prediction of clinical outcomes

		ABC	GBS	HARBINGER	p[1]	p[2]	p[3]
Mortality	AUC	0.951	0.781	0.633	0.103	<0.001	0.109
	p[4]	<0.001	0.009	0.138			
	Cut-off	>5	>12	>1			
	Sensivitiy (95% CI)	100 63.1-100	75 34.9-96.8	75 34.9-96.8			
	Specificity (95% CI)	79.5 72.8-85.2	87.5 81.7-92	52.2 44.6-59.8			
Intensive care	AUC	0.944	0.789	0.511	0.005	<0.001	<0.001
	p[4]	<0.001	<0.001	0.863			
	Cut-off	>4	>11	<2			
	Sensivitiy (95% CI)	100 83.9-100	66.6 43-85.4	95.2 76.2-99.9			
	Specificity (95% CI)	74.23 66.8-80.8	82.8 76.1-88.3	11.04 6.7-16.9			
Re-bleeding	AUC	0.733	0.704	0.510	0.698	0.013	0.014
	p[4]	<0.001	0.001	0.073			
	Cut-off	>6	>10	<0			
	Sensivitiy (95% CI)	46.6 21.3-73.4	66.6 38.4-88.2	0 0-21.8			
	Specificity (95% CI)	86.3 80.3-91.2	68.6 61.1-75.5	95.8 91.7-98.3			
Need for transfusion	AUC	0.651	0.867	0.591	<0.001	0.271	<0.001
	p[4]	<0.001	<0.001	0.029			
	Cut-off	>4	>8	>1			
	Sensivitiy (95% CI)	45.92 35.8-56.3	76.5 66.9-84.5	56.1 45.7-66.1			
	Specificity (95% CI)	79.07 69-87.1	82.56 72.9-89.9	59.3 48.2-69.8			

[1]Between ABC and GBS, [2]Between ABC and HARBINGER, [3]Between GBS and HARBINGER (Comparison of AUC), [4]Significance of AUC, AUC: Area Under The Curve

indicator that is obtained by dividing the heart rate by the systolic blood pressure. Moreover, it is the most important parameter of the HARBINGER score. Some studies have shown that the shock index is not clinically useful in predicting outcomes in upper GI bleeding (1,11), as it can only predict short-term negative results (12). In a study conducted by Horibe et al. (13), it was concluded that this score performed well in low-risk patients. This study showed that the shock index was not effective in predicting in-hospital adverse events in patients with upper GI bleeding using the HARBINGER score. It was found to be behind both the ABC score and the GBS in predicting the need for intensive care (AUC <0.511) (p<0.001).This can be due to the fact that patients with upper GI bleeding are often elderly people who suffer from chronic diseases (14). The mean age in our study was 62.4+18.8 years, which was similar to other studies. Moreover, 66.8% of the patients were taking medication to manage their chronic diseases. In similar studies, the most common chronic disease was hypertension, and in our study, it was present in 41.3% of the patients (15). Antihypertensives are known to mask the pulse and blood pressure (16,17), which affects the shock index, and therefore, the results. It is worth noting that the GBS and the HARBINGER score include hemodynamic parameters, such as heart rate and blood pressure.

Although age is not used as a parameter in either score, many studies have shown that an advanced age increases the length of stay in the intensive care unit and the risk of mortality (18). In the ABC score, age is evaluated over two points. In our study, while the cut-off value of the ABC score was >4 in predicting the need for intensive care, the AUC was 0.944. Moreover, while the same values had a cut-off value of >11 in the GBS, the AUC was 0.789, and there was a statistically significant difference between them (p=0.005). The cut-off value of the newly used ABC score in terms of the need for intensive care was previously not specified in any study. Compared to the GBS, higher AUC values, even at lower cut-off values, show how effective the ABC score is in predicting the need for intensive care.

One important parameter of the ABC score is albumin. One of the main causes of hypoalbuminemia is an increased blood loss from the GI tract (19). One of the physiological effects of albumin is the regulation of colloid osmotic pressure (20). Studies have reported that low serum albumin levels, which are common in critically ill patients, are associated with worse results (20,21). In this study, the mean albumin level of the patients in the intensive care group was 2.35±0.489 g/dL. In a meta-analysis, hypoalbuminemia was found as a prognostic biomarker (19).

Another important parameter in the ABC score is the American Society of Anesthesiologists score (ASA) classification, which evaluates patients according to their "physical health status" (22). It is valuable for showing how additional diseases are reflected in the prognosis. The absence of a chronic disease inquiry in the HARBINGER score may be the reason for the failure of this score to predict in-hospital adverse events. Upper GI bleeding, which mostly affects patients with chronic diseases and elderly patients, may present with hypovolemic shock. This situation, which concerns many systems, cannot be evaluated using a few blood parameters. The doctor's opinion of the patient is important. From this perspective, the ASA classification is a subjective system that allows the doctor to objectively evaluate the patient.

The ABC score may be more successful because it enables a subjective assessment. The ABC score and GBS were found to be effective in predicting mortality in upper GI bleeding and did not have a statistically significant difference. However, the ABC score had a higher AUC score (0.951) at a lower cut-off value (>5), whereas the HARBINGER score did not have a significant AUC level in terms of predicting mortality. The ABC score and the GBS were effective in predicting re-bleeding in terms of values under the curve, and there was no statistically significant difference between them (p=0.698). The GBS was the best predictor of the need for a blood transfusion and had a higher AUC (0.867) area (p1<0.001). In terms of in-hospital adverse events, the HARBINGER score was only effective in predicting blood transfusion (AUC =0.591 and p^4<0.05).

Stufy Limitations

The variability of the parameters among the scores makes one-on-one comparisons of the scoring systems difficult. Comparing scores with few parameters to scores with many parameters is not a fair comparison. Additionally, conducting the study retrospectively in a single center is a limitation. Patients who have hemorrhagic shock require emergency treatment faster because they are noticed earlier. Knowing which patients should be prioritized would provide us with more reliable information about the shock index.

Conclusion

This study found that the ABC score could be used to predict the need for intensive care in upper GI bleeding, and it performed better than the other scores. In addition, we concluded that using the shock index in the HARBINGER was not effective in terms of predicting in-hospital adverse events.

Ethics

Ethics Committee Approval: The approval with the number 2021/170 and date April 27, 2021 was obtained from the University Ethics Committee to allow the study to be conducted.

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: B.D., E.B.K., S.Ö., A.A., E.S., Design: B.D., E.B.K., S.Ö., A.A., E.S., Data Collection or Processing: B.D., E.B.K., S.Ö., A.A., E.S., Analysis or Interpretation: B.D., E.B.K., S.Ö., A.A., E.S., Literature Search: B.D., E.B.K., S.Ö., A.A., E.S., Writing: B.D., E.B.K., S.Ö., A.A., E.S.

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References

1. Saffouri E, Blackwell C, Laursen SB, Laine L, Dalton HR, Ngu J, et al. The Shock Index is not accurate at predicting outcomes in patients with upper gastrointestinal bleeding. Aliment Pharmacol Ther 2020;51:253-60.
2. Lanas A, Dumonceau JM, Hunt RH, Fujishiro M, Scheiman JM, Gralnek IM, et al. Non-variceal upper gastrointestinal bleeding. Nat Rev Dis Primers 2018;19:18020.
3. Nelms DW, Pelaez CA. The Acute Upper Gastrointestinal Bleed. Surg Clin North Am 2018;98:1047-57.
4. Barkun AN, Almadi M, Kuipers EJ, Laine L, Sung J, Tse F, et al. Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group. Ann Intern Med 2019;3;171:805-22.
5. Chang A, Ouejiaraphant C, Akarapatima K, Rattanasupa A, Prachayakul V. Prospective. Comparison of the AIMS65 Score, Glasgow-Blatchford Score, and Rockall Score for Predicting Clinical Outcomes in Patients with Variceal and Nonvariceal Upper Gastrointestinal Bleeding. Clin Endosc 2021;54:211-21.
6. Laursen SB, Oakland K, Laine L, Bieber V, Marmo R, Cerezo ER, et al. ABC score: a new risk score that accurately predicts mortality in acute upper and lower gastrointestinal bleeding: an international multicentre study. Gut 2021;70:707-16.
7. Horibe M, Ogura Y, Matsuzaki J, Kaneko T, Yokota T, Okawae O, et al. Absence of high-risk stigmata predicts good prognosis even in severely anemic patients with suspected acute upper gastrointestinal bleeding. United Eur Gastroenterol J 2018;6:684-90.
8. Siddiqui NS, Paul S, Khan Z, Javaid T, Hasan SS, Khan Z. Rising Events and Improved Outcomes of Gastrointestinal Bleed With Shock in USA: A 12-year National Analysis. J Clin Gastroenterol 2019;53:194-201.
9. Cannon JW. Hemorrhagic Shock. N Engl J Med 2018;25;378:370-9.
10. Standl T, Annecke T, Cascorbi I, Heller AR, Sabashnikov A, Teske W. The nomenclature, definition and distinction of types of shock. Dtsch Arztebl Int 2018;115:757-68.
11. Ratra A, Rassameehiran S, Parupudi S, Nugent K. Utility of the Shock Index and Other Risk-Scoring Tools in Patients with Gastrointestinal Bleeding. South Med J 2016;109:178-84.
12. Rassameehiran S, Teerakanok J, Suchartlikitwong S, Nugent K. Utility of the Shock Index for Risk Stratification in Patients with Acute Upper Gastrointestinal Bleeding. South Med J 2017;110:738-43.
13. Horibe M, Iwasaki E, Bazerbachi F, Kaneko T, Matsuzaki J, Minami K, et al. Horibe GI bleeding prediction score: a simple score for triage decision-making in patients with suspected upper GI bleeding. Gastrointest Endosc 2020;92:578-88.
14. Kristensen AK, Holler JG, Hallas J, Lassen A, Shapiro N. Is the shock index a universal predictor in the emergency department? A cohort study. Crit Care 2015;19:148.
15. Lee YJ, Min BR, Kim ES, Park KS, Cho KB, Jang BK. Predictive factors of mortality within 30 days in patients with nonvariceal upper gastrointestinal bleeding. Korean J Intern Med 2016;31:54-64.
16. Nativi-Nicolau J, Selzman CH, Fang JC, Stehlik J. Pharmacologic therapies for acute cardiogenic shock. Curr Opin Cardiol 2014;29:250-7.
17. Kim WY, Hongcorresponding SB. Beta-blockers in patients with septic shock: plenty of promise, but no hard evidence yet. J Thorac Dis 2016;8:1041-3.
18. Lenti MV, Pasina L, Cococcia S, Cortesi L, Miceli E, Caccia Dominioni C. Mortality rate and risk factors for gastrointestinal bleeding in elderly patients. Eur J Intern Med 2019;61:54-61.
19. Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003;237:319-34.
20. Vincent JL, Russell JA, Jacob M, Martin G, Guidet B, Wernerman J, et al. Albumin administration in the acutely ill: what is new and where next? Crit Care 2014;16;18:231.
21. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ 1998;317:235-40.
22. De Cassai A, Boscolo A, Tonetti T, Ban I, Ori C. Assignment of ASA-physical status relates to anesthesiologists' experience: a survey-based national-study. Korean J Anesthesiol 2019;72:53-9.

Original Article

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Optimal Follow-up Duration for Traumatic Multiple Rib Fractures

Travmatik Multipl Kot Kırıklarının Optimal Takip Süresi

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ABSTRACT

Objective: The rib fracture, which is one of the most common consequences of chest trauma, can cause respiratory distress, and even mortality if not properly treated. There's still limited data on the length and frequency of follow-ups in terms of the challenges that may arise after an uneventful follow-up. The focus of this research is to standardize the optimal follow-up time in patients with rib fracture.

Methods: Patients with isolated chest trauma who were admitted to the Emergency Department or were referred to the Thoracic Surgery Clinic from other hospitals within a year were included in our study. The study did not include any patients who needed thoracic intervention. Rib fracture complications were observed both during and after hospitalization.

Results: Complications did not develop in the majority of patients during hospital follow-up and discharge, but haemothorax was the most prevalent (21.4-12.2%) within the first 72 hours and at discharge.

Conclusion: Patients with rib fractures who are followed up and discharged may develop fatal consequences. When patients with recent rib fracture present to the emergency department, the emergency room physician should be alert about long-term problems.

Keywords: Rib fracture, chest trauma, follow-up, emergency room

ÖZ

Amaç: Göğüs travmasının en sık görülen sonuçlarından biri olan kaburga kırığı, uygun şekilde tedavi edilmediği takdirde solunum sıkıntısına ve hatta ölüme neden olabilir. Sorunsuz bir takipten sonra ortaya çıkabilecek zorluklar açısından takiplerin uzunluğu ve sıklığı hakkında hala sınırlı veri vardır. Bu araştırmadaki amacımız; kaburga kırığı olan hastaların optimal takip süresini standardize etmeye çalışmaktır.

Yöntemler: Çalışmamıza; bir yıllık süre içinde acil servise başvuran ve diğer hastanelerden göğüs cerrahisi kliniğine sevk edilen izole göğüs travmalı hastalar dahil edilmiştir. Toraks cerrahisine ihtiyaç duyan hiçbir hasta çalışmaya dahil edilmemiştir. Hastanedeki yatışları sırasında ve taburculuk sonrası takiplerinde hastaların kaburga kırığı komplikasyonları değerlendirilmiştir.

Bulgular: Hastaların çoğunda hastane takipleri ve taburculuk sırasında komplikasyon gelişmedi ancak ilk 72 saat içinde ve taburcu olurken en sık (%21,4-12,2) hemotoraks tespit edildi.

Sonuç: Kaburga kırığı olan hastalarda, hastane takipleri sırasında ve taburcu edildikten sonra ölümcül komplikasyonlar gelişebilir. Özgeçmişinde kaburga kırığı hikayesi olan hastalar, acil servise başvurduğunda, acil servis doktoru uzun vadede gelişebilecek komplikasyonlar konusunda uyanık olmalıdır.

Anahtar Sözcükler: Kaburga kırığı, göğüs travması, takip, acil servis

Introduction

Thoracic trauma counts up to 15% of all trauma cases consulted in emergency departments (1). Rib fractures, as the most frequent complication of blunt thoracic injuries, do not require hospitalization or further treatment at an approximate rate of 75% but may constitute the risk of developing delayed complications

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such as pneumothorax, haemothorax, or atelectasis (2-4). Mortality rates up to 30% have been reported for multiple rib fractures resulting in a flail chest and associated extra-thoracic organ injuries (5-7). Although the principle of management for a great majority of rib fractures involves analgesia and delicate observation of patients, the follow-up of outpatients is crucial to notice the potentially delayed complications.

The aim of this single-centred study was to assess the complications of multiple rib fractures in order to estimate the optimal duration of hospital stay and follow-up examinations.

Methods

A total of 68 trauma patients aged over 18 years who were admitted to the emergency unit and were thereafter referred to a thoracic surgery clinic between April 2021 and January 2022 were retrospectively analyzed. The main inclusion criteria were unilateral 3 or more rib fractures diagnosed via computerized tomography at first admission, hospitalization for at least 3 days, and attending follow-up examination 10 to 15 days after discharge. Ongoing anticoagulant therapy, development of flail chest or any extra-thoracic injuries and receiving thoracic interventions such as chest tube or pleural catheter insertion at the initial admission or surgical chest wall stabilization during the course were the main exclusion criteria. This research was approved by Kırklareli University Ethics Committee (protocol no: P20220005, date: 17.02.2022) and conducted in accordance with the Helsinki Declaration of Principles. A whole group of patients received exactly the same medication, including pantoprazole sodium, paracetamol and tramadol hydrochloride. In order to notice potential complications, vital signs were closely observed in addition to daily performed physical examinations, blood tests and chest X-rays. Discharged patients were also assessed by physical and radiological examinations at the specified periods.

Acquired data were analyzed in terms of patients' gender and age; type and side of trauma; the number of broken ribs grouped as 3-5, 6-9, and 10-12; type of complications including pneumothorax, haemothorax, pneumohemothorax, atelectasis, and subcutaneous emphysema; and elapsed time until complication listed as 0-24, 24-48, 48-72 and over 72 hours. The same complications were noted if they existed at the follow-up examinations.

Statistical Analysis

The SPSS (IBM SPSS for Windows, ver.24) statistical package program was used for calculations. Descriptive statistics for continuous variables in the study were expressed as mean and standard deviation; categorical variables were expressed as number (n) and percentage (%). Independent samples t-test was used to compare the averages of measurements and chi-square test was employed to reveal the relationship between categorical variables. P-value <0.05 was used to indicate the statistical significance.

Results

Mean age was 56.2 years among a total of 34 male (81%) and 8 female (19%) patients. A more frequent cause of injury was fall from heights whereas both hemithorax were affected evenly. A number of fractured ribs were between 3 and 5 in over half of the cases. Twenty-two patients developed distinctive complications inside of the first 72 hours. Following discharge, 2 patients developed pneumothorax and 5 haemothorax while 34 cases did not develop any complications. Related data and images of complications are detailed in Table 1 and Figure 1.

In the course of hospitalization, only one elderly patient (2.4%) died due to atelectasis and hyperacute respiratory insufficiency. Tube thoracostomy was performed in 12, pleural catheter drainage in 2 patients, whereas the other complications emerging in this period did not necessitate any additional interventions. Follow-up examination of discharged cases revealed pneumothorax in 2 and haemothorax in 5 patients who were thereafter scheduled for re-inspection since they were all asymptomatic. Complications and outcomes are summarized in Table 2.

Statistical studies showed that the development of complications during or after the hospitalization period was not related to age, gender, type and side of trauma, or the number of fractured ribs (Table 3). Besides, patients develop almost most of the complications in the first 72 hours following the traumatic event.

Discussion

The findings of this study clearly showed that majority of the complications due to traumatic rib fractures occurred in the first 72 hours and one-fifth of the patients presented with delayed complications at the follow-up examination.

Recent studies have reported mortality rates in patients with multiple rib fractures as high as 22% (8-11). Advanced age, the severity of the injury, admittance to lower levels of hospitals, and the presence of comorbid diseases were announced with elevated rates of in-hospital mortality (9-13). The mortality rate was 2.4% in this study, which might be related to the relatively lower average of patient age when compared to the ones reported in the literature.

Table 1. Clinical features of patients with traumatic rib fractures

Variables		n	%
Gender	Male	34	81
	Female	8	19
Cause of trauma	Fall from height	25	59.5
	Car accident	13	31
	Hit/crush	4	9.5
Side of trauma	Right	22	52.4
	Left	20	47.6
Number of rib fractures	3-5	24	57.1
	6-9	15	35.8
	10-12	3	7.1
Total		42	100

Figure 1. Radiological views of complications

Table 2. Complications of rib fractures, applied treatments and results

Variables		n	%
Complications for hospitalized patients	None	20	47.6
	Pneumothorax	4	9.5
	Haemothorax	9	21.4
	Haemopneumothorax	4	9.5
	Atelectasis	4	9.5
	Subcutaneous emphysema	1	2.5
Total		42	100
Elapsed time until complication (hours)	0-24	6	27.3
	24-48	7	31.8
	48-72	7	31.8
	>72	2	9.1
Total		22	100
Complication at follow-up examination	None	34	82.9
	Pneumothorax	2	4.9
	Haemothorax	5	12.2
Total		41	100

Table 3. Factors related to the development of complications

Variables		Complications during hospital stay (standard deviation)		p	Complication after discharge (standard deviation)		p
		None	Present		None	Present	
Age (mean ± standard deviation, years)		57.5±19.3	55±18.5	0.361	54.8±18.4	63.1±19.9	0.455
Gender (n)	Male	15	19	0.365	28	6	0.733
	Female	5	3		7	1	
Type of trauma (n)	Fall from height	12	13	0.651	19	6	0.125
	Car accident	7	6		12	1	
	Hit/crush	1	3		4	0	
Side of trauma (n)	Right	12	10	0.358	18	4	0.789
	Left	8	12		17	3	
Number of fractured ribs(n)	3-5	15	9	0.050	18	6	0.103
	6-9	4	11		14	6	
	10-12	1	2		3	0	

Chien et al. (10) reported that 3 or more rib fractures or any displaced fractures were good predictors of the development of complications, whereas Shulzhenko et al. (11) showed that 5 or more rib fractures were associated with increased intensive care unit admission and longer duration of stay at hospital and that 8 or more rib fractures were associated with elevated levels of complications and mortality. However, Whitson et al. (14) showed that the total number of rib fractures was not an independent predictor of in-hospital morbidity and that increased age, obesity, and accompanying traumas were the leading causes of worse outcomes. Likewise, this study revealed no connection between the number of rib fractures and the development of complications during the hospital stay or following discharge.

Several treatment strategies have been declared for rib fractures regarding the complicity and severity of pulmonary complications which are potentially evident to develop. Appropriate analgesia including catheter-based pain therapy, administration of intravenous ibuprofen or ketorolac, and also respiratory therapies featuring incentive spirometry, deep breathing, and coughing practices are recently approved as the mainstay to avoid the adverse consequences (15,16). Patients encountering life-threatening complications such as pneumothorax, and haemothorax should be instantly noticed and treated accurately. Despite the minor contradictions in timing, patient selection, and extent of surgical management of rib fractures; evidence-based data show that chest wall stabilization aids to ease the pain, reduce the incidence of pneumonia and shorten all of the durations of mechanical ventilation, hospitalization, and intensive care unit stay (17,18).

Suggestions concerning the length of follow-up differentiated between the recent studies varying from 3 to 12 months (19). This paper focused mainly on the acute and potentially fatal complications so should be extended with further long-term research to investigate the evidence of chronic complaints and disorders related to traumatic rib fractures.

Study Limitations

The principal limitation of this present study was that it was a single-center research, including a small group of cases. However, the findings support valuable and basic details for managing trauma patients with rib fractures.

Conclusion

Chest traumas lead to a high risk of mortality and morbidity. Observing patients with 3 or more traumatic rib fractures for at least 72 hours at the hospital and scheduling cases for follow-up examination between 10 to 15 days after discharge may aid to diagnose potentially life-threatening complications. Additionally, when patients with a recent rib fracture present to the emergency room, the clinician should be alert to potential complications.

Ethics

Ethics Committee Approval: This research was approved by Kırklareli University Ethics Committee (protocol no: P20220005, date: 17.02.2022) and conducted in accordance with the Helsinki Declaration of Principles.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S., Concept: O.G.,Design: O.G., Data Collection or Processing: O.G., Analysis or Interpretation: M.S., Literature Search: M.S., Writing: M.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Plourde MMD, E´ mond M, Lavoie A, Guimont C, Le Sage N, Chauny J, et al. Cohort study on the prevalence and risk factors for delayed pulmonary complications in adults following minor blunt thoracic trauma. CJEM 2014;16:136-43.
2. Parry NG, Moffata B, Vogt K. Blunt thoracic trauma: recent advances and outstanding questions. Curr Opin Crit Care 2015;21:544-8.
3. Pyke OJ Jr, Rubano JA, Vosswinkel JA, McCormack JE, Huang EC, Jawa RS. Admission of elderly blunt thoracic trauma patients directly to the intensive care unit improves outcomes. J Surg Res 2017;219:334-40.
4. Lin FC, Li R, Tung Y, Jeng K, Tsai SC. Morbidity, mortality, associated injuries, and management of traumatic rib fractures. JCMA 2016;79:329-34. Pyke OJ Jr, Rubano JA, Vosswinkel JA, McCormack JE, Huang EC, Jawa RS. Admission of elderly blunt thoracic trauma patients directly to the intensive care unit improves outcomes. J Surg Res 2017;219:334-40.
5. Bouzat P, Raux M, David JS, Tazarourte K, Galinski M, Desmettre T, et al. Chest trauma: First 48 hours management. Anaesth Crit Care Pain Med 2017;36:135-45.
6. Kaewlai R, Avery LL, Asrani AV, Novelline RA. Multidetector CT of blunt thoracic trauma. Radiographics 2008;28:1555-70.
7. Marasco S, Lee G, Summerhayes R, Fitzgerald M, Bailey M. Quality of life after major trauma with multiple rib fractures. Injury 2015;46:61-65.
8. Van Vledder MG, Kwakernaak V, Hagenaars T, Van Lieshout EMM, Verhofstad MHJ. Patterns of injury and outcomes in the elderly patient with rib fractures: a multicenter observational study. Eu J Trau Emerg Surg 2019;45:575-583.
9. Liebsch C, Seiffert T, Vlcek M, Beer M, Huber-Lang M, Wilke H. Patterns of serial rib fractures after blunt chest trauma: An analysis of 380 cases. PLoS One 2019;14:e0224105.
10. Chien CY, Chen YH, Han ST, Blaney GN, Huang TS, Chen KF. The number of displaced rib fractures is more predictive for complications in chest trauma patients. Scand J Trauma Resusc Emerg Med 2017;25:19.
11. Shulzhenko NO, Zens TJ, Beems MV, Jung HS, O'Rourke AP, Liepert AE, et al. Number of rib fractures thresholds independently predict worse outcomes in older patients with blunt trauma. Surgery 2017;161:1083-9.

12. Pressley CM, Fry WR, Philp AS, Berry SD, Smith RS. Predicting outcome of patients with chest wall injury. The Am J Surg 2012;204:910-914.
13. Marini CP, Petrone P, Soto-Sanchez A, Garcia-Santos E, Stoller C, Verde J. Predictors of mortality in patients with rib fractures. Eur J Trauma Emerg Surg 2021;47:1527-34.
14. Whitson BA, McGonigal MD, Anderson CP, Dries DJ. Increasing numbers of rib fractures do not worsen outcome: An analysis of The National Trauma Data Bank. Am Surg 2013;79:140-50.
15. Witt CE, Bulger EM. Comprehensive approach to the management of the patient with multiple rib fractures: A review and introduction of a bundled rib fracture management protocol. Trauma Surg Acute Care Open 2017;2:e000064.
16. Martina TJ, Eltoraib AS, Dunn R, Varonea A, Joycea MF, Kheirbeka T, et al. Clinical management of rib fractures and methods for prevention of pulmonary complications: A review. Injury 2019;50:1159-65.
17. Wu WM, Yang Y, Gao ZL, Zhao TC, He WW. Which is better to multiple rib fractures, surgical treatment or conservative treatment? Int J Clin Exp Med 2015;8:7930-6.
18. He Z, Zhang D, Xiao H, Zhu Q, Xuan Y, Su K, et al. The ideal methods for the management of rib fractures. J Thorac Dis 2019;11:1078-89.
19. Coughlin TA, Ng JW, Rollins KE, Forward DP, Ollivere BJ. Management of rib fractures in traumatic flail chest. Bone Joint J 2016;98-B:1119-25.

Original Article

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Sarcopenia is Associated with Postoperative Complications in Patients Undergoing D2 Gastrectomy for Gastric Cancer

Mide Kanseri Nedeniyle D2 Gastrektomi Uygulanan Hastalarda Sarkopeni Ameliyat Sonrası Komplikasyonlarla İlişkilidir

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ABSTRACT

Objective: This study aimed to investigate the relationship of sarcopenia with early postoperative complications in patients undergoing curative D2 dissection due to gastric cancer.

Methods: Patients with gastrectomy and D2 lymph node dissection for gastric cancer (GC) were retrospectively evaluated. Sarcopenia was diagnosed with computed tomography (CT) scan for pre-operative staging. Post-operative complications were determined according to Clavien-Dindo (CD) classification.

Results: Sarcopenia was seen in 59 (40.7%) of the 145 patients included in the study. The rate of overall postoperative complications in sarcopenic patients was higher than in non-sarcopenic patients. Surgical complications and medical complications were higher in sarcopenic patients. Severe surgical complications (CD Grade III and above) were significantly higher in the sarcopenia group. Sarcopenia (4.63, 95% confidence interval, 1.76-12.18; p=0.002) was a prognostic risk factor for postoperative complications.

Conclusion: Sarcopenia is associated with early postoperative complications in many types of cancer. This study showed that sarcopenia was associated with complications after D2 lymph node dissection in GC surgery. CT use in pre-operative clinical staging of patients and taking the necessary precautions make it easier to address post-operative complications.

Keywords: Sarcopenia, gastric cancer, gastrectomy, D2 lymph node dissection, postoperative complications.

ÖZ

Amaç: Bu çalışma mide kanseri (MK) nedeniyle küratif D2 lenf nodu diseksiyonu yapılan hastalarda sarkopeninin erken postoperatif komplikasyonlarla olan ilişkisini araştırmayı amaçlamaktadır.

Yöntemler: MK nedeniyle gastrektomi ve D2 lenf nodu diseksiyonu yapılan hastalar retrospektif olarak incelendi. Sarkopeni tanısı ameliyat öncesi evrelemede bilgisayarlı tomografi (BT) ile kondu. Ameliyat sonrası komplikasyonlar Clavien-Dindo (CD) sınıflamasına göre belirlendi.

Bulgular: Sarkopeni, çalışmaya katılan 145 hastanın 59'unda (%40,7) görüldü. Sarkopenik hastalarda ameliyat sonrası komplikasyon oranı sarkopenik olmayanlara göre daha yüksekti. Cerrahi ve medikal komplikasyonlar sarkopenik hastalarda daha yüksekti. Ciddi cerrahi komplikasyonlar (CD evre 3 ve üzeri) sarkopeni grubunda anlamlı olarak daha yüksekti. Sarkopeni (4,63, %95 güven aralığı, 1,76-12,18; p=0,002) postoperatif komplikasyonlar için prognostik bir risk faktörüdür.

Sonuç: Sarkopeni birçok kanser türünde erken postoperatif komplikasyonlarla ilişkilidir. Bu çalışma, mide kanseri cerrahisinde sarkopeninin D2 lenf nodu diseksiyonu sonrası komplikasyonlarla ilişkili olduğunu göstermiştir. Hastaların ameliyat öncesi klinik evrelemesinde BT kullanımı ve gerekli önlemlerin alınması ameliyat sonrası komplikasyonların ele alınmasını kolaylaştırmaktadır.

Anahtar Sözcükler: Sarkopeni, mide kanseri, gastrektomi, D2 lenf nodu diseksiyonu, ameliyat sonrası komplikasyonlar

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Introduction

Gastric cancer (GC) is the fifth most commonly diagnosed malignancy and the third leading cause of cancer-related deaths among all cancers (1). After discussing for a long time, radical gastrectomy and D2 lymph node dissection in locally advanced GC was considered as standard surgical treatment in the western and eastern worlds (2,3). Despite advances in perioperative care and surgical techniques, after gastric resection and D2 dissection, postoperative mortality (5%) and morbidity (62%) rates are still high (4-6). In many studies, advanced age, presence of comorbidity/comorbidities, high body mass index (BMI), and malnutrition have been defined as risk factors for postoperative complications after GC surgery (7-9).

Rosenberg first described sarcopenia as age-related progressive skeletal muscle (SM) loss (10). The current definition by the European Working Group on Sarcopenia in Older People (EWGSOP) and The Asian Working Group for Sarcopenia state that sarcopenia is a syndrome that involves a decrease in a generalized loss of muscle mass, muscle strength, and function (11,12). Although sarcopenia is mainly seen in older ages; it can also be seen at an early age along with malnutrition, inactivity, and cancer. Patients with GC have a high risk of developing sarcopenia due to intestinal obstruction, vomiting, and decreased food intake (11).

Routine computerized tomography (CT) is performed in pre-operative clinical staging in cancer patients. Especially in clinical trials, CT is defined as one of the most recommended methods for diagnosing sarcopenia (11,12). Sarcopenia is diagnosed by calculating the SM index (SMI) from axial sections that pass through the third lumbar vertebrae (L3) (13,14). Sarcopenia is known to adversely affect early post-operative complications and survival in different types of cancer (15,16).

Several studies have reported that sarcopenia causes an increase in early postoperative complication rates in GC (14,17-19). Increased complication rates lead to prolonged hospital stays and increases in costs, mortality, and morbidity. In some studies involving populations of patients who were operated due to GC, the prevalence of sarcopenia was reported as high compared to other abdominal surgical oncology populations, but sarcopenia was not associated with postoperative morbidity or mortality (20).

This study aimed to investigate whether sarcopenia is associated with early postoperative complications in patients who have had gastrectomy and D2 lymph node dissection with the diagnosis of GC in our clinic.

Methods

Ethical committee approval (2018-980) was obtained from Okmeydanı Training and Research Hospital. Patients with locally advanced gastric adenocarcinoma that underwent surgery for consecutive curative purposes between January 2013 and June 2020 were retrospectively evaluated. Patients over 18 years of age, histological type of gastric adenocarcinoma, and an Eastern Cooperative Oncology Group performance score (0-2) were considered as the inclusion criteria for the study. Metastatic patients and those with second primary cancer were not included in the study. Based on CT findings, patients were divided into two groups consisting of sarcopenic and non-sarcopenic patients. The same surgical team performed curative gastric resection and D2 lymph node dissection. Roux en Y anastomosis was preferred for reconstruction. Complication data were retrieved from the prospectively generated database. Complications that developed within the 30 days of surgery were considered early postoperative complications. Early postoperative complications and duration of hospital stay were evaluated. Post-operative complications were evaluated according to Clavien-Dindo (CD) Classification (21). Grades I and II were identified as mild and Grade III and above as severe complications. Complications were defined as surgical complications that were directly related to the surgical field. Systemic complications that developed outside the surgical area were defined as medical complications. Severe complications were considered based on the CD scans when more than one complication was seen in the same patient. Operative mortality was assessed as death within the first 30 days of the postoperative period or deaths due to post-operative complications. Tumor staging was performed according to the American Joint Committee on Cancer Staging 8th edition (22).

The CT images taken within three weeks of pre-operative staging or re-staging in patients receiving neoadjuvant therapy were evaluated. CT evaluation was performed by radiologists experienced in gastrointestinal tract radiology. The assessment was carried out by transferring images to high-resolution medical monitors with picture archiving communication systems. Three consecutive axial CT images with a thickness of 5 mm were taken, passing through the upper, middle, and lower levels of the lumbar vertebra (L3) corpus. Using advanced image processing methods on these three sections, the muscles were separated from other tissues by selecting Hounsfield Unit (HU) values -29 and +150 HU. The muscles on the chosen section (rectus abdominus, transversus abdominus, external oblique, internal oblique, psoas, erector spina, and quadratus lumborum) were manually painted in a different color, and the surface measurement of the muscles was obtained (Figure 1A and B). The surface of the muscles was then expressed as cm2 by obtaining the average of these three separate sections. INFINITT software (version 3.0.11.3, INFINITT Healthcare Co. Ltd., Seoul, Korea) was used for this measurement. The surface area of these muscles (cm^2) was divided into the square of the patient's height, and the total skeletal musculoskeletal mass index (SMI =cm^2/m^2) was obtained. BMI and different cut-off values by gender were used to diagnose sarcopenia. Male patients with a BMI ≥25 and an SMI below 53 cm^2/m^2 or a BMI of <25 and SMI <43 cm2/m2 were accepted as sarcopenic. In women, patients with SMI below 41 cm^2/m^2 were considered sarcopenic (20,23).

Statistical Analysis

Statistical analysis of data was obtained using the Statistical Package for the Social Sciences (SPSS)22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk,

NY: IBM Corp.) program. The mean ± standard deviation was used as descriptive statistics when summarizing variables. The Student's t-test or Mann-Whitney test was used for continuous variables when making cross-group comparisons. In evaluating categorical data, the chi-square test was used for binary variables. We assessed the prognostic effects of sarcopenia-related parameters on complications. We analyzed clinical and pathological factors that affected complications. For this, we applied the logistic regression model 24. Post-operative complications and clinicopathological factors affecting these complications were analyzed together with multivariable logistic regression models. Each parameter was analyzed individually. Results were defined as odds ratios and 95% confidence interval (CIs), and a p-value <0.05 was considered statistically significant.

Results

The mean age of the 145 study patients was 60.2±12.2, and 98 were males (67%). Fifty-nine (40.7%) patients were sarcopenic. Thirty-seven out of 80 patients receiving neoadjuvant therapy were sarcopenic. No differences in terms of age, BMI, tumor localization, type of surgery, histological differentiation, and tumor stage between sarcopenic and non-sarcopenic patients were noted.

The mean SMI of the patients was 38 (29-52) in the sarcopenic and 51 (41-66) in the non-sarcopenic groups.

Demographic and clinical patient information are given in Table 1. Of 145 patients, 60 patients had subtotal, and 85 patients had total gastrectomy. All patients underwent curative R0 resection, D2 dissection, and Roux N Y esophagojejunostomy/gastrojejunostomy anastomosis. The mean operative time was 225 minutes, and no difference between sarcopenic and non-sarcopenic patients was found. The mean number of lymph nodes removed was 36 (10-83).

Post-operative complications are shown in Table 2. The total number of patients with at least one post-operative complication was 36 (24.8%). The postoperative complication rate was significantly higher in the sarcopenic group (42.4%) than in the non-sarcopenic group (12.8%; p=0.008). Most of the complications (n=25) were mild (<grade III). The surgical complication rate was 20.7%, and the medical complication rate was 4.1%. The most common mild complication was wound as infection (n=13). Of these 11 patients with severe complications, nine were surgical (≥ CD grade III), and two were medical complications. The most common severe surgical complication was pancreatic fistula (n=4). Eight of the patients who developed severe surgical complications were in the sarcopenic group, and a statistically significant difference between the groups was found (p=0.009). Medical, surgical, and overall complications in sarcopenic and nonsarcopenic patients are shown in Figure 2. The number of patients who underwent repeat surgeries was three. One patient underwent three repeat surgeries for an anastomotic leak and pancreatic fistula. Two patients underwent repeat surgery, one with intra-abdominal bleeding and the other with anastomotic leakage. Two of the three patients who underwent repeat surgeries were in the sarcopenic group. Mortality occurred in three patients (2.1%). On the seventh postoperative day, a patient died due to myocardial infarction, one patient died of pulmonary embolism on the sixth day, and one died on the 39th day due to anastomotic leakage.

The median hospital stay was 8.5 (6-49) days in the non-sarcopenic group and 12.9 (5-155) in the sarcopenic group. A statistically significant difference between the two groups was found in terms of hospital stay (p=0.008).

Univariate and multivariate analysis results associated with complications are shown in Table 3. Multivariate logistic regression analysis was performed according to age, sex, duration

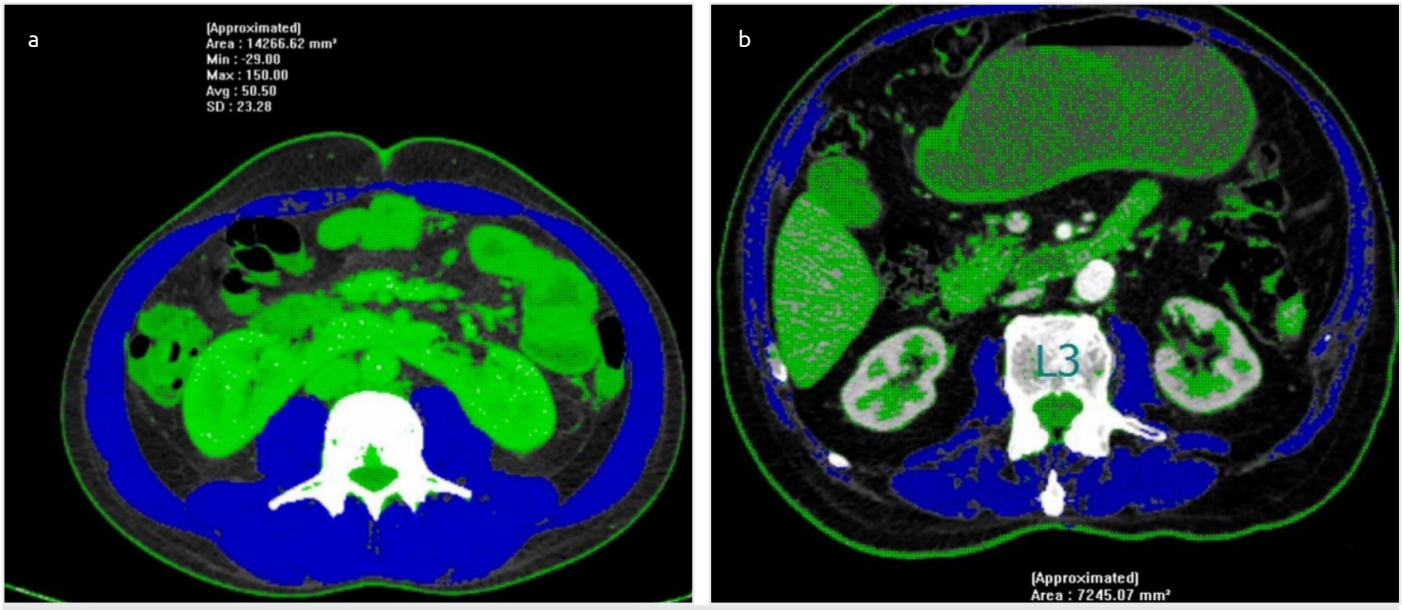

Figure 1. a) Non-sarcopenic patient CT image, b) Sarcopenic patient CT image

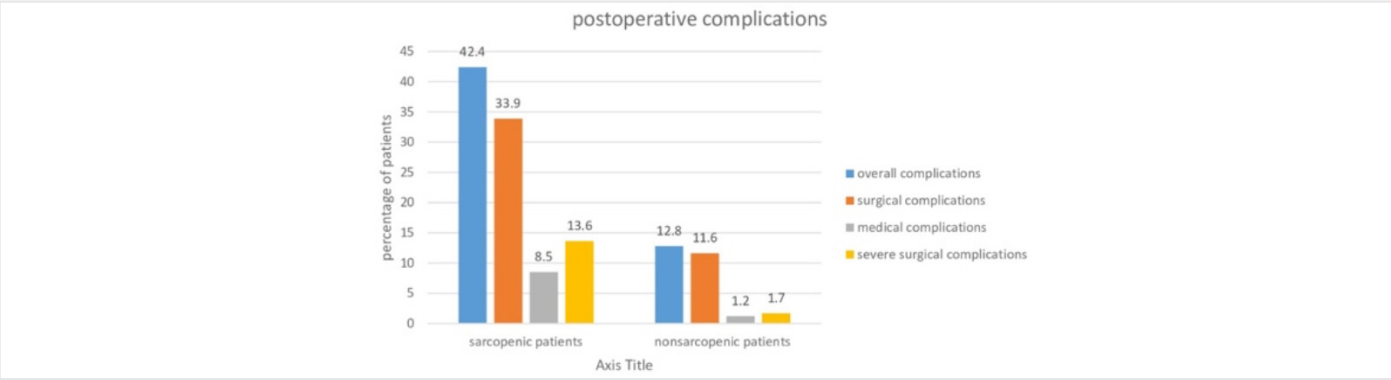

Figure 2. Incidence of overall, surgical, medical and severe surgical complications in sarcopenic and non-sarcopenic patients

Table 1. Patients' demographic and clinicopathological futures

	Sarcopenia (n=59)	Non-sarcopenia (n=86)	All (n=145)	p value
Age (years)	61.7±12.5	59.1±12.0	60.2±12.2	0.161
Sex Male Female	 30 (50.8) 29 (49.2)	 68 (79.1) 18 (20.9)	 98 (67.6) 47 (32.4)	0.0001
Preoperative chemotherapy	37 (62.7)	43 (50.0)	80 (55.2)	0.09
Additional organ resection	7 (11.9)	12 (14.0)	19 (13.1)	0.45
BMI (kg/m^2)	25.0 (18.0-32.0)	24.9 (18.6-43.0)	25.0 (18.0-43.0)	0.97
SMI (cm^2/m^2)	38.0 (29.0-52.0)	51.0 (41.0-66.0)	46.0 (29.0-66.0)	0.0001
Histologic type Well differentiated Moderately differentiated Undifferentiated	 9 (15.3) 18 (30.5) 32 (54.2)	 14 (16.3) 29 (33.7) 43 (50.0)	 23 (15.7) 47 (32.4) 75 (51.7)	0.88
Tumor location Cardia Corpus Antrum	 16 (27.1) 21 (35.6) 22 (37.3)	 16 (18.6) 27 (31.4) 43 (50.0)	 32 (22.1) 48 (33.1) 65 (44.8)	0.11
TNM stage Stage I Stage II Stage III Stage IV*	 14 (23.7) 21 (35.6) 21 (35.6) 3 (5.1)	 23 (26.7) 23 (26.7) 37 (43.0) 3 (3.4)	 37 (25.5) 44 (30.3) 58 (40.0) 6 (4.1)	0.61
Type of gastrectomy Total gastrectomy Subtotal gastrectomy	 38 (65.5) 21 (36.2)	 47 (54.7) 39 (45.3)	 85 (58.6) 60 (41.4)	0.30
Operation duration (minutes)	225 (180-360)	225 (150-360)	225 (150-360)	0.87
Tumor size (cm)	4.0 (0.2-13)	4.0 (0.1-20)	4.0 (0.1-20)	0.20
Number of harvested lymph nodes	33 (10-79)	37 (13-83)	36 (10-83)	0.45
Length of hospital stay (days)	12.9 (5-155)	8.5 (6-49)	10.3 (95-155)	0.008

BMI: Body mass index, SMI: Skeletal muscle index
Data presented as mean ± standard deviation, median (1st-3rd quartiles) or n (%).
*: Malignant cells in peritoneal washings

of surgery, sarcopenia, tumor stage, neoadjuvant chemotherapy, gastrectomy type, additional organ resection, tumor diameter, and total number of removed lymph nodes. Sarcopenia (4.63, 95% CI 1.76-12.18, p=0.002) emerged as an independent prognostic factor for postoperative complications.

Discussion

Studies related to sarcopenia are rapidly increasing. Standardization, cut-off values, and diagnostic criteria should be determined. The EWGSOP and Asian Sarcopenia Study groups have defined new diagnostic criteria for sarcopenia (11,12). CT is one of the diagnostic methods that can be used to diagnose sarcopenia. Since we used CT in the clinical staging of pre-operative tumors in our patients, we diagnosed sarcopenia according to these values. Sarcopenia rates are shown in the literature over a wide range from 12.5% to 72.2%. (14,18,20,25). The different rates in these studies vary depending on the selected cut-off values. In our study, we found that the sarcopenia rate was 40.7%.

Systemic inflammation, hyper-catabolism, and nutritional disorders lead to sarcopenia regardless of age in cancer patients. Sarcopenia causes an increase in postoperative complication rates in studies of different cancer patients (26,27). Although GC surgery is the most effective treatment for the disease, postoperative complication rates are high (4-6). GC is a biologically aggressive tumor. Patients cannot get enough calories due to obstruction or neoadjuvant treatment in the pre-operative period. Due to insufficient caloric intake and the effect of the tumor on the inflammatory system, patients with GC also have a high risk of sarcopenia development (14,18,20). In studies, sarcopenia caused an increase in the rates of early postoperative complications in patients who underwent surgery for gastric adenocarcinoma (14,17-19,28). In our study, patients in both groups underwent the same surgical approach by the same surgical team. Our total complication rate (p=0.008) and surgical complication rates (CDIII) ≥ were higher in sarcopenic patients (p=0.009).

When postoperative hospital stay is evaluated, the average hospital stay in sarcopenic patients is longer (25). We found that the sarcopenic group had a higher hospital stay (p=0.008).

In a study of 152 patients, Tegels showed that the sarcopenia rate was 57.7%, but it did not increase the risk of post-operative complications (20). In this study by Tegels, the curative resection rate was 69.7%, and the results might be associated with a low curative resection rate. In our study, curative resection and D2 lymph node dissection were performed to all patients.

Advanced age, malnutrition, and decreased physical activity are among the causes of sarcopenia (11). In our study, no difference in terms of age between the sarcopenic and nonsarcopenic groups was found. Considering that the elderly population will increase and patients will have GC in older age, evaluating these patients for sarcopenia and taking necessary precautions will help reduce post-operative complications. Pre-operative calorie and protein intake in sarcopenic patients are significantly lower than in non-sarcopenic patients. Providing adequate pre-operative calorie and protein support to these patients can reduce postoperative complication rates. A decrease in muscle strength in patients with sarcopenia leads to impaired physical performance, decreased cardiopulmonary capacity, impaired endothelial function, and decreased tissue oxygenation (29,30). These issues will negatively affect wound healing. In our study, respiratory physiotherapy and nutritional support were administered to all patients during the pre-operative period depending on their nutritional status. Pre-operative regular repeated physical exercise and nutrition support programs have the potential to reduce sarcopenia

Table 2. Postoperative complications

	Sarcopenia n=59 (%)	Non-sarcopenia n=86 (%)	All n=145 (%)	p value
All postoperative complications	25 (42.4)	11 (12.8)	36 (24.8)	**0.008**
All surgical complications	20 (33.9)	10 (11.6)	30 (20.7)	
Wound complications	7 (11.9)	6 (7.0)	13 (9.0)	
Intra-abdominal bleeding	1 (1.7)	1 (1.2)	2 (1.4)	
Anastomotic leakage	1 (1.7)	1 (1.2)	2 (1.4)	0.084
Chylous leakage	6 (10.2)	2 (2.3)	8 (5.5)	
Pancreatic fistula	4 (6.8)	1 (1.2)	5 (3.4)	
Evisceration	1 (1.7)	-	1 (0.7)	
All medical complications	5 (8.5)	1 (1.2)	6 (4.1)	
Miyocardial infarction	1 (1.7)	-	1 (0.7)	0.041
Pneumonia	3 (5.1)	1 (1.2)	4 (2.8)	
Pulmonary embolism	1 (1.7)	-	1 (0.7)	
Severe surgical complications ≥ grade-III	8 (13.6)	1 (1.7)	9 (6.2)	**0.009**
Severe medical complications	2 (3.4)	0	2 (1.4)	0.66
Mortality	2 (3.4)	1 (1.2)	3 (2.1)	0.36
Length of hospital stay (days)	12.9 (5-155)	8.5 (6-49)	10.3 (5-155)	**0.008**

Data presented as mean ± standard deviation, median (1st-3rd quartiles) or n (%)

and improve the postoperative clinical condition, especially in patients with malnutrition (29,30). Before surgery, the focus should be on improving postoperative clinical outcomes.

Study Limitations

The single-center nature was the main limitation of our study. Multicenter studies with a large number of patients are needed. In addition, the evaluation of sarcopenia diagnosis not only with CT but also with the parameters of muscle strength and physical performance should be supported (11).

In this study, we found that sarcopenia caused an increase in postoperative complications after D2 lymph node dissection in GC surgery. As a result, it can be said that the diagnosis of preoperative sarcopenia could be effective in terms of the development of postoperative complications. Diagnosing pre-operative sarcopenia with CT, which is used in patients' pre-operative clinical oncologic staging, and taking the necessary precautions can make it easier to deal with postoperative complications.

Conclusion

Sarcopenia, diagnosed by CT findings, is an independent risk factor for postoperative complications after D2 gastrectomy for locally advanced gastric adenocarcinoma. The early postoperative complications were higher in sarcopenic patients. Before surgery, the focus should be on improving sarcopenia to reduce post-operative complications.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Okmeydanı Training and Research Hospital (date: 11.09.2018/no: 980).

Peer-review: Externally peer reviewed.

Table 3. Univariable and Multivariable analysis of factors associated with complications

	No complications (n=109)	Complications (n=36)	pvalue	Odds Ratio (95% CI, p value)
Age (years)	60.5±12.5	59.4±11.6	0.65	0.99 (0.95-1.04, p=0.818)
Sex				
Male	74 (75.5)	24 (24.5)	0.523	1.13 (0.41-3.18, p=0.811)
Female	35 (74.5)	12 (25.5)		
Sarkopenia				
Yes	34 (57.6)	25 (42.4)	**0.0001**	**4.63 (1.76-12.18, p=0.002)**
No	75 (87.2)	11 (12.8)		-
Preoperative chemotherapy				
Yes	52 (65)	28 (35)	**0.001**	**4.64 (1.56-13.80, p=0.006)**
No	57 (87.7)	8 (12.3)		-
Tumor localisation				
Cardia	21 (65.6)	11 (64.4)	0.12	
Corpus	34 (70.8)	14 (29.2)		0.69 (0.21-2.32, p=0.551)
Antrum	54 (83.1)	11 (16.9)		0.07 (0.01-0.65, p=0.267)
Type of gastrectomy				
Total	60 (70.6)	25 (29.4)	0.092	0.10 (0.01-13.7, p=0.356
Subtotal	49 (81.7)	11 (18.3)		
Additonal organ resection				
Yes	18 (94.7)	1 (5.3)	0.024	0.07 (0.01-0.65, p=0.020)
No	91 (72.2)	35 (27.8)		
Operationduration (minutes)	219 (150-360)	240 (180-360)	0.36	1.00 (0.99-1.01, p=0.948)
TNM STAGE				
Stage I	28 (75.7)	9 (24.3)		1.37 (0.39-4.79, p=0.619)
Stage II	28 (63.6)	16 (36.4)	0.1	0.52 (0.12-2.19, p=0.371)
Stage III	47 (81.0)	11 (19.0)		-
Stage IV	6 (6)	0 (0)		-
Tumor size (cm)	4 (0.1-20)	3.4 (0.2-12)	0.21	0.94 (0.77-1.14, p=0.514)
Number of harvestedlymphnodes	35 (10-83)	40.5 (18-78)	0.18	1.02 (0.99-1.06, p=0.203

CI: Confidence interval, BMI: Body mass index, SMI: Skeletal muscle index.
Data presented as mean ± standard deviation, median (1^{st}-3^{rd} quartiles) or n (%). Multivariable analysis, Univariable analysis

Authorship Contributions

Surgical and Medical Practices: A.A., Ö.B., İ.Y., Concept: S.K., Design: S.D.Ö., S.E., Data Collection or Processing: Ö.B., R.Y.B., Analysis or Interpretation: R.Y.B., S.D.Ö., S.K., Literature Search: A.A., İ.Y., M.G.D., Writing: A.A., İ.Y., M.G.D.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21.
3. Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(SUPPL.6):vi57-63.
4. Gertsen EC, Goense L, Brenkman HJF, van Hillegersberg R, Ruurda JP. Identification of the clinically most relevant postoperative complications after gastrectomy: a population-based cohort study. Gastric Cancer 2020;23:339-48.
5. Selby LV, Vertosick EA, Sjoberg DD, Schattner MA, Janjigian YY, Brennan MF, et al. Morbidity after total gastrectomy: Analysis of 238 patients. J Am Coll Surg 2015;220:863-71.e2.
6. Li SS, Costantino CL, Mullen JT. Morbidity and Mortality of Total Gastrectomy: a Comprehensive Analysis of 90-Day Outcomes. J Gastrointest Surg 2019;23:1340-8.
7. Deguchi Y, Fukagawa T, Morita S, Ohashi M, Saka M, Katai H. Identification of risk factors for esophagojejunal anastomotic leakage after gastric surgery. World J Surg 2012;36:1617-22.
8. Shin HS, Oh SJ, Suh BJ. Factors related to morbidity in elderly gastric cancer patients undergoing gastrectomies. J Gastric Cancer 2014;14:173-9.
9. Guner A, Kim SY, Yu JE, Min IK, Roh YH, Roh C, et al. Parameters for Predicting Surgical Outcomes for Gastric Cancer Patients: Simple Is Better Than Complex. Ann Surg Oncol 2018;25:3239-47.
10. Rosenberg IH. Sarcopenia: Origins and clinical relevance. In: Journal of Nutrition. Vol 127. American Society for Nutrition; 1997.
11. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
12. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc 2020;21:300-7.e2.
13. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629-35.
14. Beuran M, Tache C, Ciubotaru C, Vartic M, Hostiuc S, Prodan A, et al. Sarcopenia is a predictive factor for postoperative morbidity and mortality in patients having radical gastrectomy for cancer. Chir 2018;113:678-86.
15. Vergara-Fernandez O, Trejo-Avila M, Salgado-Nesme N. Sarcopenia in patients with colorectal cancer: A comprehensive review. World J Clin Cases 2020;8:1188-202.
16. Voron T, Tselikas L, Pietrasz D, Pigneur F, Laurent A, Compagnon P, et al. Sarcopenia impacts on short- and long-term results of hepatectomy for hepatocellular carcinoma. Ann Surg 2015;261:1173-83.
17. O'Brien S, Twomey M, Moloney F, Kavanagh RG, Carey BW, Power D, et al. Sarcopenia and post-operative morbidity and mortality in patients with gastric cancer. J Gastric Cancer 2018;18:242-52.
18. Zhuang CL, Huang DD, Pang WY, Zhou CJ, Wang SL, Lou N, et al. Sarcopenia is an independent predictor of severe postoperative complications and long-term survival after radical gastrectomy for gastric cancer: Analysis from a large-scale cohort. Medicine (Baltimore) 2016;95:e3164.
19. Huang DD, Zhou CJ, Wang SL, Mao ST, Zhou XY, Lou N, et al. Impact of different sarcopenia stages on the postoperative outcomes after radical gastrectomy for gastric cancer. Surg (United States) 2017;161:680-93.
20. Tegels JJ, van Vugt JL, Reisinger KW, Hulsewé KW, Hoofwijk AG, Derikx JP, et al. Sarcopenia is highly prevalent in patients undergoing surgery for gastric cancer but not associated with worse outcomes. J Surg Oncol 2015;112:403-7.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
22. AJCC Cancer Staging Manual | Mahul B. Amin | Springer.
23. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013;31:1539-47.
24. Zhang Z. Model building strategy for logistic regression: Purposeful selection. Ann Transl Med 2016;4.
25. Wang SL, Zhuang CL, Huang DD, Pang WY, Lou N, Chen FF, et al. Sarcopenia Adversely Impacts Postoperative Clinical Outcomes Following Gastrectomy in Patients with Gastric Cancer: A Prospective Study. Ann Surg Oncol 2016;23:556-64.
26. Oh RK, Ko HM, Lee JE, Lee KH, Kim JY, Kim JS. Clinical impact of sarcopenia in patients with colon cancer undergoing laparoscopic surgery. Ann Surg Treat Res 2020;99:153-60.
27. Boshier PR, Heneghan R, Markar SR, Baracos VE, Low DE. Assessment of body composition and sarcopenia in patients with esophageal cancer: A systematic review and meta-analysis. Dis Esophagus 2018;31.
28. Kudou K, Saeki H, Nakashima Y, Edahiro K, Korehisa S, Taniguchi D, et al. Prognostic Significance of Sarcopenia in Patients with Esophagogastric Junction Cancer or Upper Gastric Cancer. Ann Surg Oncol 2017;24:1804-10.
29. Yamamoto K, Nagatsuma Y, Fukuda Y, Hirao M, Nishikawa K, Miyamoto A, et al. Effectiveness of a preoperative exercise and nutritional support program for elderly sarcopenic patients with gastric cancer. Gastric Cancer 2017;20:913-8.
30. Lopes KG, Bottino DA, Farinatti P, de Souza MDGC, Maranhão PA, de Araujo CMS, et al. Strength training with blood flow restriction – a novel therapeutic approach for older adults with sarcopenia? A case report. Clin Interv Aging 2019;14:1461-9.
31. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int 2017;28:1817-33.

Original Article

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Patient Safety in the Surgery: An Investigation of the Near-miss Cases Encountered by the Surgical Team While Applying the Surgical Safety Checklist

Cerrahide Hasta Güvenliği: Cerrahi Ekibinin Güvenli Cerrahi Kontrol Listesini Uygularken Karşılaştığı Ramak Kala Olayların İncelenmesi

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ABSTRACT

Objective: The study was conducted as a descriptive study in order to investigate the near-miss events that surgical team members encountered during the use of the Surgical Safety Checklist (SSC).

Methods: The research was carried out between June 25, 2018 and September 7, 2018 in the surgical services and operating theaters of three public hospitals in Ankara. The sample of the study (n=387) was consisted of surgical team members working in the surgical services (n=94) andin the operating room (n=293) (anesthesiologist, nurse, surgeon, surgical technician, anesthesia technician). Data were obtained with the individual data sheet and SSC application form. Chi-square test and Mann-Whitney U test were used for statistical analysis ($p<0.05$).

Results: As a result of the research, it was determined that 27.1% of the surgical team members working in surgical service and operating rooms did not receive training on the SSC. It was found that 72.9% of surgical team members received training on SSC and 37.0% said that there were near-miss cases and medical errors that were prevented with the use of SSC. Although 90.2% of the participants knew the near-miss definition and 37.0% encountered them, the rate of those reporting the event was determined as 7.8%. The near-miss cases most commonly encountered by the participants in the study were found to be absence of side marking in 26.0%, not removing jewelry in 23.0%, and being full of the patient (eating before surgery) in 18.0%. In addition, carelessness in 26.2%, crowd

ÖZ

Amaç: Araştırma, cerrahi ekip üyelerinin Güvenli Cerrahi Kontrol Listesi'nin (GCKL) kullanımı sırasında karşılaştığı ramak kala olayları incelemek amacıyla tanımlayıcı olarak yapılmıştır.

Yöntemler: Araştırmanın katılımcılarını, 25 Haziran 2018-07 Eylül 2018 tarihleri arasında Ankara ilinde bulunan üç kamu hastanesinin, cerrahi servisleri (n=94) ve ameliyathanede çalışan (n=293) cerrahi ekip üyeleri (anestezi uzmanı, hemşire, cerrah, cerrahi teknisyen, anestezi teknikeri) oluşturmuştur (n=387). Veriler Bireysel Bilgi Formu ve GCKL Uygulama Formu ile elde edilmiştir. Veriler değerlendirilirken ki-kare testi ve Mann-Whitney U testi kullanılmıştır ($p<0,05$).

Bulgular: Araştırma sonucunda, cerrahi servis ve ameliyathanelerde çalışan cerrahi ekip üyelerinin %27,1'i GCKL ile ilgili eğitim almadığı belirlenmiştir. Cerrahi ekip üyelerinin %72,9'unun GCKL ile ilgili eğitim aldığı, %37,0'ının ise GCKL'nin kullanımı sırasında bu uygulamanın önlediği ramak kala olaylar ve tıbbi hatalar olduğunu ifade ettiği bulunmuştur. Ramak kala olayı %90,2'sinin bilmesine ve karşılaşanların oranın %37,0 olmasına karşın, olay bildirimi yapanların oranı %7,8 olarak saptanmıştır. Araştırmaya katılanların en çok karşılaştığı ramak kala olaylar %26 ile taraf işaretlemenin olmaması, %23 ile takıların çıkarılmaması, %18 ile hastanın tok gelmesi olarak saptanmıştır. Ayrıca tıbbi hata oluşum nedeni olarak %26,2 oranında dikkatsizlik, %10,1 oranında yoğunluk ve %14,8 oranında bilgi eksikliği bildirilmiştir.

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in 10.1%, and lack of information in 14.8% were reported as the causes of medical errors.

Conclusion: As a result of the study, it was determined that surgical team members, especially nurses with high rates of use faced with near-miss cases during the use of SSC. Early detection of these errors will prevent the occurrence of preventable medical errors. Increasing training and making positive feedback to surgical team members will increase the use of SSC form and event notifications.

Keywords: Surgery, SSC, patient safety, near-miss case

Sonuç: Araştırma sonucunda, cerrahi ekip üyelerinin, özellikle kullanım oranı yüksek olan hemşirelerin GCKL'yi kullanımı sırasında ramak kala olaylar ile karşılaştığı belirlenmiştir. Önlenebilir tıbbi hataların erken saptanması bu hataların oluşumunu engelleyecektir. Konu ile ilgili eğitimlerin artırılması ve cerrahi ekip üyelerine olumlu geri bildirimler yapılması GCKL formunun daha çok kullanımını ve olay bildirimlerinin artmasını sağlayacaktır.

Anahtar Sözcükler: Cerrahi, GCKL, hasta güvenliği, ramak kala olay

Introduction

The concept of patient safety has emerged with the reporting of medical errors. With the Institute of Medicine report, which was the institution where human errors and adverse events were reported in the United States and England since 2000, hospital records in the USA, Australia and the United Kingdom were examined and it was stated that the average error rate was 10%. According to this result, the subject of patient safety in health services has been put into practice. Thus, patient safety has become a permanent part of health policy (1). With these developments in patient safety, a patient safety culture has been tried to be created in healthcare professionals. Various studies have been carried out for this purpose and the knowledge, clinical practice styles, attitudes and perceptions of the surgical team about patient safety have been evaluated. In this way, it is aimed to reduce medical errors (2). The main purpose of the surgical team in health services is expressed as maximizing the patient's safety and well-being through evidence-based practices, effective communication and cooperation, and thus optimizing people's quality of life (3-5).

The approach to patient safety is applied according to the "find and fix" model. When a situation that threatens patient safety is detected, the aim is not to stigmatize or judge, but to identify the steps where things go wrong and to minimize the number of errors as much as possible. In order to achieve this, it is necessary to facilitate work flexibility and try to increase the quality of service, to appreciate success and increase motivation, and to raise awareness to avoid undesirable results and medical errors (6). In order to improve the quality of medical services, instead of blaming the people associated with the error, it is necessary to focus on identifying the factors underlying human error, these factors are expressed as device error, environmental factors, inappropriate institutional policies, physical workload, and lack of information (7,8).

It has been determined that there is a need for safety reporting systems (SRS) in order to reduce medical errors in the health system and to take safety precautions (9). The Agency for Healthcare Research and Quality states that the "name, blame and judge" approach is not effective in medical errors (9). It is stated that in the security reporting system, the understanding of de-identification, that is, anonymization, is an important element for the increase of medical error notifications, and approaches to the reporting of medical errors in health systems focus on the error itself, not who has caused the error. It has been determined that the failure to provide adequate de-identification conditions at the error reporting stage prevents the formation of the reporting system (10). In the event and near-miss event notification, the events in which the patients and employees have been harmed or the events that are detected without causing harm are reported. For example, events such as stab wounds, falls, wrong side marking, lack of patient preparation for surgery, incomplete testing and lack of identity verification are events that should be reported (11,12).

Near misses are often ignored and not reported. However, if it is taken seriously and if it is known that it has parallel consequences with medical errors, possible medical errors can be prevented. The idea of reporting undesirable events and negative results has been considered as a situation accepted by many sectors for many years. In the aviation industry, in 1975, errors or "near misses" that should be reported without blaming individuals and with giving them confidence were defined as events that did not cause harm, even though they were close (13). Notifications made by the employees to prevent the reoccurrence of the events experienced are important in terms of shedding light on the measures to be taken in the future. A hospital employee who sees or experiences all kinds of events (near misses or undesired events) that may threaten patient and employee safety is responsible for reporting (14,15).

In Turkey, SRS was put at the disposal of health institutions in 2016 in order to report errors that occured in the pharmaceutical, laboratory and surgical processes. With the completion of the development of the patient safety module, patient safety errors can also be entered into the system on August 31, 2016. It was reported that a total of 74383 error notifications were made to the SRF in 2016. Of these, 93.8% were found to be laboratory errors, 1.5% to patient safety errors, 1.6% to surgical errors, and 3.1% to medication errors. These reported errors are used to develop Quality Standards in Health, and as a result, it is aimed to prevent errors related to the health care process (16). As a result of Sheikhtaheri's study in Iran in 2014, it was determined that reporting of medical errors increased the number of successful practices in error management as well as identifying weaknesses (17). The hesitations in the reporting system and the lack of error reporting are important risks in terms of patient safety, and

the number of surgical interventions in the world is too high to be underestimated. It is stated that 234.2 million invasive procedures and interventions are performed every year in the world (18). Considering the high rate of worldwide surgical interventions and high mortality and morbidity rates, it has been determined that the lack of safe surgical steps is an important health problem and cannot be neglected (18).

With the World Health Organization (WHO) motto "Safe Surgery Saves Lives", the Safe Surgery Checklist (SSC) was created on February 9, 2009, and the WHO Guidelines for Safe Surgery was chaired by Professor Atul Gawande. Its purpose has been to provide a simple, effective set of priority controls to improve teamwork and communication and to encourage active consideration of patient safety for every operation performed. Professor Gawande's team observed over 3000 patients prior to implementation of the checklist and approximately 4000 patients after implementation of the checklist. It was reported that the total mortality rate was 1.5% before the initiation

Table 1. The results of the surgical team members' information and notification regarding near-miss events (n=387)

Features	Doctor (n=82)		Nurse (n=277)		Other** (n=28)		Total		Analysis (n=387)	
	n	%	n	%	n	%	n	%	x²*	P
The state of knowing near miss event										
Yes	77	93.9	247	89.2	25	89.3	349	90.2	1.6	0.443
No	5	6.1	30	10.8	3	10.7	38	9.8		
Near-miss event reporting status										
Yes	6	7.3	23	8.3	1	3.6	30	7.8	0.8	0.662
No	76	92.7	254	91.7	27	96.4	357	92.2		

*Chi-square test, p<0.05 **Surgical technician, anesthesia technician (n=28)
Table 2 shows the results of the relationship between the situations of encountering near-miss events and the unit where they worked. As a result of the research, it was determined that 37.0% of the surgical team members encountered a near-miss event

Table 2. Results on the relationship between the situations of encountering near misses and the profession (n=387)

The situation of encountering a near-miss event in the use of SSC	Doctor		Nurse		Other**		Total		Analysis*	
	n	%	n	%	n	%	n	%	x²	P
Yes	25	30.5	109	39.4	9	32.1	143	37.0	2.47	0.291
No	57	69.5	168	60.6	19	67.9	244	63.0		
Total	82	100.0	277	100.0	28	100.0	387	100.0		

*Chi-square test, p<0.05 **Surgical technician, anesthesia technician
Table 3 shows the situations where the surgical team members encountered near-miss events. Near-miss events encountered by the surgical team were not confirming the site of surgery in 26.0%, not removing jewelry and prostheses in 23.0%, and being full (eating before surgery) of the patient in 18.0%

Table 3. Distribution of findings related to near misses encountered by surgical team members (n=100)

Near-miss events	Doctor (n=21)		Nurse (n=71)		Other** (n=8)		Total (n=100)	
	N	%	n	%	N	%	n	%
Allergy	1	4.8	4	5.6	4	50.0	9	9.0
Deficiencies in preparation for surgery	0	0.0	3	4.2	0	0.0	3	3.0
Anticoagulant use	0	0.0	1	1.4	0	0.0	1	1.0
Missing examination	0	0.0	1	1.4	0	0.0	1	1.0
Being full (eating before surgery) of the patient	2	9.5	16	22.5	0	0.0	18	18.0
Incorrect blood transfusion to the patient	0	0.0	0	0.0	1	12.5	1	1.0
Not authenticating	2	9.5	8	11.3	0	0.0	10	10.0
Lack of consent	0	0.0	3	4.2	0	0.0	3	3.0
Lack of counting and pathology control	1	4.8	1	1.4	1	12.5	3	3.0
Inappropriate sterilization	0	0.0	2	2.8	0	0.0	2	2.0
Failure to remove jewelry and prosthesis	10	47.6	13	18.3	0	0.0	23	23.0
Not confirming the site of surgery	5	23.8	19	26.8	2	25.0	26	26.0
Total	21	100	71	100	8	100	100	100

*Chi-square test, p<0.05 **Surgical technician, anesthesia technician (n=28)

of SSC and decreased to 0.8% after SSC application, while inpatient complications decreased from 11% to 7% after using SSC (19-21). All these studies show that safe surgery saves lives in order to ensure patient safety (20,21). The WHO's SSC was approved by nearly 246 institutions in more than 40 countries in the America, Europe, Africa and Asia. The WHO estimates that five hundred thousand deaths per year can be prevented with the application of SSC (22-25). In order to ensure patient safety, prevent and reduce medical errors; the International Joint Commission included the prevention of wrong-sided surgery and surgery on the wrong patient within the scope of the patient safety targets of the year 2014 (26-29).

The purpose of developing SSC is to help reduce the number of errors in surgical practice, strengthen accepted safety practices, and improve interdisciplinary communication and teamwork. The SSC is designed as a tool for use by clinicians to increase the safety of their operations and reduce unnecessary surgical death and complications. Its use has been significantly associated with significant reductions in complication and mortality rates and improvements in basic care standards (29-31). SSC is a process that should start from the moment the patient is admitted to the service. The list was renewed by the Ministry of Health with the permission of WHO of "Every institution can regulate SSC according to its needs and procedure" and it was published in 2011 under the name of "Safe Surgery Checklist TR". SCC, which consists of three stages in accordance with WHO's own needs, includes the clinical process with the idea that "the surgical process begins in the clinic" in our country and consists of four stages (32,33).

As a result of the researches, there are studies examining the application and functionality of SCC (19,34-36). In these studies, who used the SCC more, usage rates, whether it was applied correctly, the rate of application, and missing aspects that could not be applied were examined (34-38). However, near-misses during the use of GCKL have not been studied. Based on this requirement, our study was conducted to describe the near-miss events encountered during the application of GCCL in the operating room and surgical wards by the surgical team. It is thought that this research will reveal the importance of the use of the form by revealing the near misses that the use of GCKL prevents, as well as eliminating this deficiency.

Methods

Sample of the Research

This research was planned as a descriptive study to examine the near-miss events encountered by surgical team members (nurses, surgeons, anesthesiologists, anesthesia technicians and surgical technicians) working in surgical units while performing SCC. The population of the research consisted of 560 surgical team members working in the surgical wards and operating room units of three public hospitals in Ankara. In this study, the sample selection was not made, and the whole universe was tried to be reached. It was planned to include all surgical team members in the study. The sample of the study consisted of 387 surgical team members who voluntarily agreed to participate in the study and completed the questionnaire. One hundred twenty surgical team members who were not on active duty in these hospitals due to various reasons (maternity leave, assignment, etc.) at the time the research was conducted, and 53 surgical team members who did not complete the questionnaire and did not agree to participate in the research were not included in the study.

Ethical Aspect of Research

Ethics committee approval was obtained from the Ankara Yıldırım Beyazıt University Social and Human Sciences Ethics Committee for the research (decision number: 36, date: 23.02.2018). Written institutional approval was obtained from three public hospitals to implement the study. Participation in the research was on a voluntary basis, and an Informed Consent Form was signed by the healthcare professionals within the scope of the survey, which contained information about the purpose and content of the research.

Data Collection Forms

Data collection form consisting of two parts, based on the literature review, was used to collect the research data. In the first part, there is the "Individual Information Form" consisting of 10 questions, which includes the individual characteristics of the surgical team members working in the surgical units. In the second part, the "Safe Surgery Checklist Application Form" consisting of 45 questions used by the surgical team members working in the surgical units, including SCC and near-miss event reporting, was used (2,18,23,33,39-41). The data collection form was prepared after being submitted to the opinion of two experts working in the Surgical Diseases Nursing program of two different universities and started to be implemented.

Application Phase of the Research

Between the dates of the research, a total of 440 surgical team members working actively in the public hospital were reached. Data collection form consisting of two parts, based on the literature review, was used to collect the research data. In the first part, there was the "Individual Information Form" consisting of 10 questions, which included the individual characteristics of the surgical team members working in the surgical units. In the second part, the "Safe Surgery Checklist Application Form" consisting of 45 questions used by the surgical team members working in the surgical units, including SCC and near-miss event reporting, was used (2,18,23,33,39-41). The data collection form was prepared after being submitted to the opinion of two experts working in the Surgical Diseases Nursing program of two different universities and started to be implemented. After obtaining institutional approvals, the purpose of the study was explained to 440 surgical team members working in the surgical wards and operating room units, and their written and verbal consents were obtained, and the data collection form was delivered in a personalized sealed envelope. Information was given about making the data collection form individually and it was applied on condition that it was received two weeks later. The data were collected by the closed envelope method between

June 2018 and October 2018, and 387 participants who applied the forms were included in the application.

Analysis of Data

The data obtained in this study were analyzed with the SPSS 21 package program. Number, percentage, mean, standard deviation, minimum and maximum values were used to represent the descriptive variables. In the data obtained, Mann-Whitney U test was used for two-group mean comparisons and chi-square analysis was used for dependency tests of categorical variables. In statistical analysis, the level of significance was accepted as $p<0.05$. The non-parametric Mann-Whitney U test was used in case the data did not show normal distribution. $P<0.05$ was used as the significance level, and it was stated that there was a significant difference in the case of $p<0.05$, and no significant difference in the case of $p>0.05$.

Results

Of the participants in the study, 76.7% are women. Of the participants, 75.7% worked in the operating room and 24.3% in the surgical service. Of the employees in the operating room participating in the research, 67.52% were nurses. The number of surgical service personnel participating in the research was 94, and 90 of 94 personnel were nurses. Of the nurses participating in the research, 61.7% had a bachelor's degree and 14.8% had a master's degree. There was no significant difference between occupational groups in terms of age ($p>0.05$). While the duration of the profession was significantly longer in nurses, the longest duration in the unit was again in nurses ($p<0.05$). The average tenure of the nurses participating in the study was 11.12 years. Nurses had the longest tenure in the unit they worked, with an average of 6.41 years. It was determined that 93.9% of the surgeons participating in the study had information about the near miss event on the wrist, and 89.2% of the nurses had information about the near miss event. While surgeons reported 6 events, nurses reported 23 events.

Discussion

The research was carried out to examine the near-miss (avoidable) events encountered by surgical team members working in surgical units and operating rooms during the use of SSC. In the literature, obstacles related to the application of SSC, changes in surgical error rates, changes in morbidity rates, changes in mortality rates, and team cohesion were evaluated. There are a limited number of studies showing that it prevents many errors during the use of the form before surgical errors occur. For this reason, the results of the research were discussed by comparing with the studies and literature information (41-44).

The SSC was first defined by WHO between 2007 and 2008, drawing attention to patient safety with the "Safe Surgery Saves Lives" campaign. Thanks to this campaign, many application guides were created and revised according to usage over time (42,43,45,46). Delgado Hurtado et al. (45) showed that 93.80% of healthcare professionals (surgeons, anesthesia, nurses, assistants) had knowledge about SSC. In our study, this rate was 94.57%. The results of our study were parallel to the results of other studies. The reason for this may be supporting the training of health workers with seminars, congresses, training and interpersonal communication and keeping the issue up to date with SRS audits.

When participation in scientific studies, evaluation of health personnel who supported the study, and participation in patient safety issues were evaluated Carvalho et al. (47), it was determined that nurses' perception of participation in scientific studies and patient safety was 60%. The participation rate of the nurses in our study among the health personnel working in the surgical units was determined as 71.58%. It is thought that in-service training should be increased in order for the whole team to have patient safety awareness.

In the systematic review study of Weieser et al. (48), it was concluded that the patients received surgical care, but the measurement of safety and quality of care was not a priority, and the safety criteria should be evaluated systematically. Parallel to this, in our study, it was determined that the surgical team members were knowledgeable about the reporting of a near-miss event, but the reporting rate was low despite encountering a near-miss event. Surgical team members should be guided and supervised regarding event notification recording systems.

In a study, 3301 surgical applications selected from 63 hospitals in Sweden were analyzed. Near-miss events encountered in these surgical patients were analyzed and it was concluded that adverse events were common and preventable in surgical care (49). In our study, parallel to this study, healthcare professionals thought that medical errors could be prevented with SSC. Near misses have parallel results with medical errors, and sharing these data with the surgical team will increase awareness about reporting.

In the study published in Brazil in 2019, nurses' perspective on the use of SSC was evaluated. As a result of the questionnaire administered to 220 nurses via e-mail, it was determined that the nurses were committed to the surgical intervention goals, but failure was identified in the prevention of events (50). In our study, although it was observed that healthcare professionals gave importance to safe surgery, failure was found in reporting. Undeclared events will not be resolved as long as they are limited to the knowledge of the individuals and will cause new errors to occur.

In the study published by Ramsey et al. (52) in 2019, significant decreases were found in mortality rates due to the use of SSC in 2000s. Since the implementation of the checklist, there has been a reduction in perioperative deaths as part of an overall national safety strategy (51). In our study, the most important causes of medical errors were found to be carelessness and crowd. SSC is seen as a safety step that helps to reduce the rate of medical errors and mortality that may increase in inattention and crowd.

Schwendimann et al.'s (52) study on the global use of the WHO Surgical Safety Checklist to ensure patient safety during surgery demonstrated that extensive local expert interviews and individual, procedural, and contextual variables influenced the

implementation of the checklist. Facilitating factors included well-informed experts advocating the use of the checklist and teams focused on the intended process and content of the checklist. In contrast, factors such as staff distrust, a generally negative attitude towards the checklist, lack of teamwork, and hesitation to complete the checklist prevented its implementation (52). In our study, there were findings parallel to this result. Crowd and lack of time were thought to affect usage. Instead of seeing SCC as a workload, it should be considered as an indispensable part of surgery and inspections should be increased.

In the meta-analysis study in which the effect of the use of SCC and the complications it prevented were investigated; 9 studies showed an increase in the rate of patient identification, an increase in the rate of surgery side marking, and a decrease in the rate of reoperation (40,43). The results we found in our study also showed parallel results with the literature. Near-miss events encountered during the use of SCC were wrong surgery side in 14.91% and unconfirmed surgery side in 8.71%. These parallel results reveal the importance of using SCC.

In order to contribute to the creation of safe hospitals in the study of Moy et al. (53), a questionnaire was applied to a total of 290 participants including 50 or more personnel from occupational groups directly involved in patient care and service processes. Of the participants, 96.90% stated that they knew what a near-miss event was, 91.03% of them stated that they defined a near-miss event related to patient safety, 81.72% of them correctly defined a near-miss event, 16.90% of health workers stated that they experienced/observed a near-miss event, but it was shown that 69.77% of those events were not reported (53). In the study of Kaplan et al. (54), malpractice cases were examined between 2003 and 2008 and it was reported that midwives caused injury to the newborns due to their carelessness and inexperience while applying the phenylketonuria test (54). In the study of Karagözoğlu et al. (55), the rates of encountering and reporting medication errors of 204 nurses were evaluated. As a result, it was reported that although 62.30% of them encountered medication errors, 80.40% did not report any errors, and the most common medication error was incorrect medication administration. In that study, it was concluded that the majority of the nurses had a lack of knowledge about error reporting and a negative opinion about the attitude of the management about medical errors was dominant (55). Although 37.0% of the near-misses were encountered in our study, the reporting rate was 7.8%. As a result, studies should be carried out to increase the reporting of near miss incidents related to patient and employee safety, analysis results and measures taken should be shared with employees in order to ensure that reporting and near-miss notifications play a role in preventing errors. These shares will contribute positively to the creation of a safe hospital environment.

When we looked at the number of notifications in the surgical field among a total of 74,383 notifications made to the SRS in 2016, the followings were reported; not marking the surgical site in 346, not confirming identity, surgery site and procedure in 130, not removing make-up, prosthesis and valuables in 104, not shaving the operation area in 54, not being a healthcare worker during patient transfer in 52, not checking consent in 50, not checking the side in 45, not getting the consent of the patient in 38, not checking the marking in 32, and not confirming preoperative fasting in 27 (56). Parallel to the results of SRS, in our study, the rate of near miss during surgery side verification was the highest with 14.69%. This result shows that near misses and medical errors have parallel consequences. As a result, reporting near-miss events as medical errors will reduce the rate of medical errors. Restricting this information to the person will not be beneficial in terms of patient safety, which will lead to a vicious circle. The importance of revealing the defect in the system, not by whom the mistake has been made, should be emphasized and the possible concerns of the members of the surgical team should be addressed. Encouraging the reporting of near misses through studies will increase the number of notifications and raise awareness.

Study Limitations

Since the research was conducted in three public hospitals in Ankara, its findings could not be generalized.

Conclusion

In line with the results obtained from our study, in-service training on the use of SCC and raising awareness of patient safety should be increased. Controls related to the application part should be increased. Education should be provided on how near-miss event reporting reduces the occurrence of surgical errors. It should be ensured that the awareness of healthcare professionals working in surgical units is provided to prevent medical errors rather than revealing errors and punishing the employee. It is recommended to implement SCC, which improves team members' communication, cooperation and patient safety in the perioperative process.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ankara Yıldırım Beyazıt University Social and Human Sciences Ethics Committee for the research (decision number: 36, date: 23.02.2018).

Informed Consent: Participation in the research was on a voluntary basis, and an Informed Consent Form was signed by the healthcare professionals within the scope of the survey, which contained information about the purpose and content of the research.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: H.T., Design: H.T., Analysis or Interpretation: S.B., H.T., Literature Search: S.B., Writing: S.B., H.T.

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References

1. Sevdalis N, Hull L, Birnbach DJ. Improving patient safety in the operating the atre and perioperative care: obstacles, interventions, and priorities for accelerating progress. Br J Anaesth 2012;109 Suppl 1:i3-i16.
2. deElguea JO, Orkaizagirre A, de Miguel MS, Urcola F, Germán C, Lizaso I. Adapting and validating the Hospital Survey on Patient Safety Culture (HSOPS) fornursing students (HSOPS-NS): A new measure of Patient Safety Climate. Nurse Educ Today 2019;75:95-103.
3. Mortell, M. Is There a Theory–Practice–Ethics Gap? A Patient Safety Case, Study. International Journal of Africa Nursing Sciences 2019;10:38-42.
4. James JT. A New, evidence-based estimate of patient harms associated with hospital care. J Patient Saf 2013;9:122-8.
5. Leape LL. Hospital readmissions following surgery: turning complications into "treasures". JAMA 2015;313:467-8.
6. Braithwaite J, Wears RL, Hollnagel E. Resilienthealthcare: turning patient safety on itshead. Int J Qual Health Care 2015;27:418-20.
7. Adams JL, Garber S. Reducing medical malpractice by targeting physicians making medical malpractice payments. JELS 2007;4:185-222.
8. Bogner MS. Human Error in Medicine: A Frontier for Change. In Human error in Medicine 2018;S:373-83.
9. Institute of Medicine (IOM) ToErr is Human: Building A Safer Health System, *National Academy Press,* 2000, Washington. 20.05.2019.
10. Sağlık Bakanlığı (2017) *Güvenlik Raporlama Sistemi*. http://grs.saglik.gov.tr/Default.aspx. 20 Mayıs 2019.
11. World Health Organization. WHO Draft Guidelines for Adverse Event Reportingand Learning Systems: From in formationtoaction 2005. https://apps.who.int/iris/bitstream/handle/10665/69797/WHO-EIP-SPO-QPS-05.3-eng.pdf?sequence=1&isAllowed=y. 15 Mart 2019;59.
12. World Health Organization. WHO Draft Guidelines for Adverse Event Reportingand Learning Systems: World alliance for patient safety. https://apps.who.int/iris/bitstream/handle/10665/69797/WHO-EIP-SPO-QPS-05.3-eng.pdf?sequence=1&isAllowed=y. 15 Mart 2019;75.
13. Mallory S, Weller J, Bloch M, Maze M. The individual, the system, and medical error. BJA CEPD Reviews 2003;3:179-82.
14. Oyebode F. Clinical errors and medical negligence. Med Princ Pract 2013;22:323-33.
15. Eadie A. Medical error reporting should it be mandatory in Scotland. J Forensic Leg Med 2012;19:437-41.
16. Sağlık Bakanlığı Güvenlik Raporlama Sistemi (GRS) 2016 Yılı İstatistik ve Analiz Raporu, Sağlıkta Kalite ve Akreditasyon Daire Başkanlığı, 2016, Ankara.
17. Sheikhtaheri A. Near-misses and their importance for improving patient safety. Iran J Public Health 2014;43:853-4.
18. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: A modelling strategy based on available data. Lancet 2008;372:139-44.
19. Woodman N, Walker I. World Health Organization Surgical Safety Checklist. 2016.
20. Borchard A, Schwappach DL, Barbir A, Bezzola P. A systematicreview of theeffectiveness, compliance, and critical factors for implementation of safety checklists in surgery. Ann Surg 2012;256:925-33.
21. Christian CK, Gustafson ML, RothEM, Sheridan TB, Gandhi TK, Dwyer K, et al. A prospective study of patient safety in the operating room. Surgery 2006;139:159-73.
22. Ragusa PS, Bitterman A, Auerbach B, Healy WA. Effectiveness of surgical safety checklist in improving patient safety. Orthopedics 2016;39:307-10.
23. Anonymous. Checklist improves surgical safety. The Canadian Nurse 2009;105:8.
24. Catalano K. The World Health Organization's surgical safety checklist. Plastic Surgical Nursing 2009;29:124-7.
25. Beaumant K, Russell J. Standardising forreliability: the contribution of tool sand checklists. Nurs Stand 2012;26:35-9.
26. Sağlık Bakanlığı ve Akreditasyon Daire Başkalığı (2013) Cerrahide bilinen 10 gerçek.http://www.kalite.saglik.gov.tr/index.php?lang=tr&page =225. 18 Ocak 2018.
27. Cheek DJ, JonesTS. Safety surgery initiative saves lives. Nursing 2009;39:14-5.
28. Leape LL, Woods DD, Hatlie MJ, Kizer KW, Schroeder SA, Lundberg GD. Promoting patient safety by preventing medical error. JAMA 1998;280:1444-7.
29. WHO Patient Safety & World Health Organization. WHO guidelines for safe surgery. http://www.who.int/iris/handle/10665/44185. 1 Nisan 2019.
30. Najari F, Mostafazadeh B, Natanzi LS. Complications of Laparoscopic and Laparotomy Surgeries in the Department of Tehran Legal Medical Committee in 2011-2016. International Journal of Medical Toxicology and Forensic Medicine 2019;9:83-90.
31. Karakachian A, Colbert A. Nurses' Moral Distress, Burnout, and Intentions to Leave: An Integrative Review. J Forensic Nurs 2019;15:133-42.
32. Pauniaho S, Lepojarvi M, Peltomaa K, Saario I, Isojarvi A, Malmivaaro A. A surgical checklist ıncreases patient safety. 2009.
33. PerformansYönetimiveKaliteGeliştirmeDaireBaşkanlığı(2011).Cerrahi Güvenlik Kontrol Listesi Uygulama Kılavuzu. http://dosyasb.saglik.gov.tr/Eklenti/4333,guvenlicerrahikontrollistesiuygulamarehberipdf.pdf. 4 Nisan 2019.
34. Haugen AS, Søfteland E, Almeland SK, Sevdalis N, Vonen B, Eide GE, et al. Effect of the World Health Organization checklist on patient outcomes: a stepped wedgecluster randomized controlledtrial. Ann Surg 2015;261:821-8.
35. Bergs J, Hellings J, Cleemput I, Zurel Ö, De Troyer V, Van Hiel M, et al. Systematic review and meta-analysis of the effect of the World Health Organization surgical safety checklist on postoperative complications. Br J Surg 2014;101:150-8.
36. Behzadifar M, Behzadifar M, Jahanpanah F, Bragazzi NL. Patient safety culture assessment in Iran usingthe "Hospitalsurvey on patient safety culture" tool: A systematic reviewand meta-analysis. CEGH 2019;7:641-7.

37. Pittet D, Allegranzi B, Storr J, Donaldson L. 'Cleancare is safer care': The global patient safety challenge 2005-2006. Int J Infect Dis 2006;10:419-24.

38. Zahiri HR, Stromberg J, Skupsky H, Knepp EK, Folstein M, Silverman R, Singh D. Prevention of 3 "neverevents" in theoperatingroom: fires, gossypiboma, andwrong-site surgery. Surg İnnov 2011;18:55-60.

39. Binazir MB, Alizadeh M, Nikasa P, Azhough R, Movassaghi R. The effect of a modified World health organization surgical safety checklist on postoperative complications in a tertiary hospital in İran, 2012. Iran J Public Health 2016;13:21-7.

40. Sewell M, Adebibe M, Jayakumar P, Jawett C, Kong K, Vemalapalli K, Levack B. Use of the WHO surgical checklist in traumaand orthopaedic patients. Int Orthop 2011;35:897-901.

41. Delgado-Hurtado JJ, Jimenez X, Penalonzo PA, Villatoro C, İzquierdo S, Cifuentes M. Acceptance of the WHO surgical safeyt checklist among surgical personnelin hospitals in Guatemala City. BMC Health Serv Res 2012;12:169.

42. Weiser TG, Haynes AB, Dziekan G, Berry WR, Lipsitz SR, Gawande AA; Fort he safe surgery saves lives in vestigators and study group, affect of a 19-item surgical safety checklist during urgent operationsin a global patient population. Ann Surg 2010;251:976-80.

43. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al. A surgical safety checklist toreduce mobidityand mortality in a global population. N Engl J Med 2009;360:491-9.

44. Alfredsdottir H, Bjprnsdottir K. Nursing and patient safety in the operating room. J Adv Nurs 2008;61:29-37.

45. Delgado-Hurtado JJ, Jimenez X, Penalonzo PA, Villatoro C, İzquierdo S, Cifuentes M. Acceptance of the WHO surgical safeyt checklist among surgical personnelin hospitals in Guatemala City. BMC Health Serv Res 2012;12:169.

46. Nwosu A. The horror of wrong-side surgery continues: report of two cases in a regional trauma centre in Nigeria, Patient Saf Surg 2015;9:6.

47. Carvalho PA, Göttems LBD, Pires MRGM, Oliveira MLCD. Safety culture in the operating room of a public hospital in the perception of health care professionals. Rev Latino-Am Enfermagem 2015;23:1041-8.

48. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, et al. Size and distribution of the global volume of surgery in 2012. Bull World Health Organ. 2016;94:201-9F.

49. Nilsson L, Risberg MB, Montgomery A, Sjödahl R, Schildmeijer K, Rutberg H. Preventable adverse events in surgical care in Sweden: a nation widereview of patient notes. Medicine (Baltimore) 2016;95:e3047.

50. DeSiqueira Gutierres L, dosSantos JLG, Barbosa SDFF, Maia ARC, Koerich C, Gonçalves N. Adherencetothe objectives of the Safe Surgery Saves Lives Initiative: perspective of nurses. Rev Latino-Am Enfermagem 2019;27.

51. Ramsay G, Haynes AB, Lipsitz SR, Solsky I, Leitch J, Gawande AA, et al. Reducing surgical mortality in Scotland by use of the WHO Surgical Safety Checklist. Br J Surg 2019;106:1005-11.

52. Schwendimann R, Blatter C, Lüthy M, Mohr G, Girard T, Batzer S, et al. Adherencetothe WHO surgical safety checklist: an observational study in a Swiss academic center. Patient Saf Surg 2019;13:14.

53. Moy EB, Akkor A, Aydın Ö, Çelik N, Cankuş B , Mamur C, Karagülle M. Near miss incidents; what is the reason: disregard or lack of information? Online Türk Sağlık Bilimleri Dergisi 2018;3:70-86.

54. Kaplan S, Çelik S, Şahin S, Pınar G. Evaluation of cases of nursing and midwifery malpractice discussed between 2003 and 2008 in high health council. Balkan Med J 2014;2:7-11.

55. Karagözoğlu Ş, Meryem OTU, Coşgun G. Reporting of Thoughts and Drug Errors of Nurses For Notice of Drug Errors in A Research and Practice Hospital. Cumhuriyet Üniv Sağ Bil Enst Derg 2019;4:26-39.

56. İncesu E, Orhan F. An analysis of security reporting system data in a public hospital: A retrospective research. Health Care Acad J 2018;5:79-86.

Case Report

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Merkel Cell Carcinoma

Merkel Hücreli Karsinom

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare tumor that arises from mechanoreceptor Merkel cells. Ultraviolet exposure, immunosuppression and Merkel cell polyoma virus play a significant role in tumor pathogenesis. Although it typically presents as an initially indolent growing, painless solitary lesion, the course of MCC may be aggressive due to the nodal invasion, distant metastasis and high recurrence rates. We presented a case of MCC with a background history of rheumatoid arthritis treated with immunosuppressive therapy for many years who had necrotizing granulomatous lymphadenitis.

Keywords: Merkel cell carcinoma, immunosuppression, therapy

ÖZ

Merkel hücreli karsinom (MKK), mekanoreseptör Merkel hücrelerinden kaynaklanan nadir bir tümördür. Ultraviyole maruziyeti, immünosupresyon ve Merkel hücreli polyoma virüsü, tümör patogenezinde önemli bir rol oynamaktadır. Tipik olarak başlangıçta yavaş büyüyen, ağrısız soliter bir lezyon olarak ortaya çıkmasına rağmen, MKK'nin seyri nodal invazyon, uzak metastaz ve yüksek nüks oranları nedeniyle agresif olabilir. Geçmişinde romatoid artrit öyküsü bulunan, uzun yıllardır immünosupresif tedavi gören ve nekrotizan granülomatöz lenfadeniti olan bir MKK olgusunu sunuyoruz.

Anahtar Sözcükler: Merkel hücreli karsinom, immünosupresyon, tedavi

Introduction

Merkel cell carcinoma (MCC) is an aggressive primary neuroendocrine cutaneous tumor that arises from mechanoreceptor Merkel cells (1).

Although MCC is a rare tumor, incidence of MCC has tended to increase in seniors in the last two decades. This higher prevelance of MCC seen in seniors may be explained with immunosenescence. Because, immune system plays a key role in tumorigenesis of MCC (2).

Due to the local recurrence and early regional and distant metastasis tendencies of MCC, early diagnosis and treatment may increase survival rates (3).We presented a 65-year-old female immunosuppressed patient who was treated with wide excision, regional lymph dissection, radiotherapy and chemotherapy.

Case Report

A 65-year-old female patient was admitted to the dermatology clinic with a non-tender, solitary and fast-growing lesion which was reddish purple in color and 3x4 cm in size on her right malar region that had been present for 4 months (Figure 1 a, b). The result of a punch biopsy was reported as a neuroendocrine tumor and the patientwas referred to our clinic.

The initial neck examination was negative for lymphadenopathy.

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She reported that she had been diagnosed as having rheumatoid arthritis (RA) in 1999, and treated with 30 mg/day prednisolone. Routine abdominal ultrasonography which had been performed in 2009 revealed the growth of lymph nodes, hence prednisolone's dose was reduced from 30 mg/day to 15 mg/day and hydroxychloroquine sulphate was added with a dose of 400 mg/day with a suspicion of sarcoidosis. She has used prednisolone 7.5 mg/day since 2015 and the dosage has been increased due to the attacks.

Biopsy of the tumoral mass revealed that the number of mitosis was 52/mm^2, there were widespread lymphovascular invasion and slight lymphocyte infiltration. Nodular and infiltrative tumor growth pattern was observed, and the depth of the tumor was extended to the subcutaneous adipose tissue. Lastly, MCC was diagnosed following the exclusion of other neuroendocrine tumors, radiologically.

A positron emission tomography (PET) scan was performed to rule out a metastasis of a neuroendocrine tumor, and a lymphadenopathy in the posterior pectoral muscle area was revealed.

Under the general anesthesia, the tumor mass on the right malar region was excised with 1.5 cm surgical margin and a skin substitute patch (Epigard®, Biovision) was applied to the excised area. The lymph node was removed by a thoracic surgeon. The pathology of the tumor was reported as MCC, and the biopsy of the removed lymph node was reported as a necrotizing granulomatous lymphadenitis (Figure 1 c,d,e). The surgical margin of the tumor base was found to be closer than 0.1 cm and re-excision was performed. The defect area was repaired with a Mustardé flap and a full-thickness graft which was harvested from the left supraclavicular region. After the wound healing process, the patient was treated with quadruple anti-tuberculosis (TB) therapy regimen (ethambutol 1.5 g/day, rifampicin 600 mg/day, pyrazinamide 2 g/day, isoniazide (INH) 300 mg/day) for two months. Subsequently, double anti-TB treatment regimen (rifampicin 600 mg/day and INH 300 mg/day) was applied and the treatment period was completed to a year and successful result was obtained from the specified treatment.

One week after the initiation of anti-TB treatment, 5,400 cGy radiotherapy was applied in 30 fractions.

One week after the onset of radiotherapy regimen, chemotherapy was started and performed on the 1st, 8th and 15th days of every 21-day periods, cisplatin 40 mg/m^2 was applied for 3 coursesand etoposide 100 mg/m^2 was applied for 3 courses.

There was no recurrence and local-distant metastasis at 60-month follow-up (Figure 1 f, g).

Discussion

The MCC is more common in white race and males over 65 years of age. Ultraviolet exposure, immunosuppression and Merkel cell polyoma virus (MCPyV) play a significant role in tumor pathogenesis (4,5).

Immunosuppression is thought to be an important risk factor for MCC. Immunosuppressed patients; especially those with hematological malignancy, HIV, autoimmune disease and organ transplants, are at high risk for developing MCC (6,7).

Our patient had RA and sarcoidosis. She received systemic steroid treatments because of these diseases. In our patient, we think that both autoimmune diseases and their treatments play a role in the development of MCC by causing immunosuppression.

The MCCs are located in the head and neck region, extremities and trunk. As in our case, there is a painless, firm, pinkish purple, solitary, and glossy nodule which is rapidly growing in a

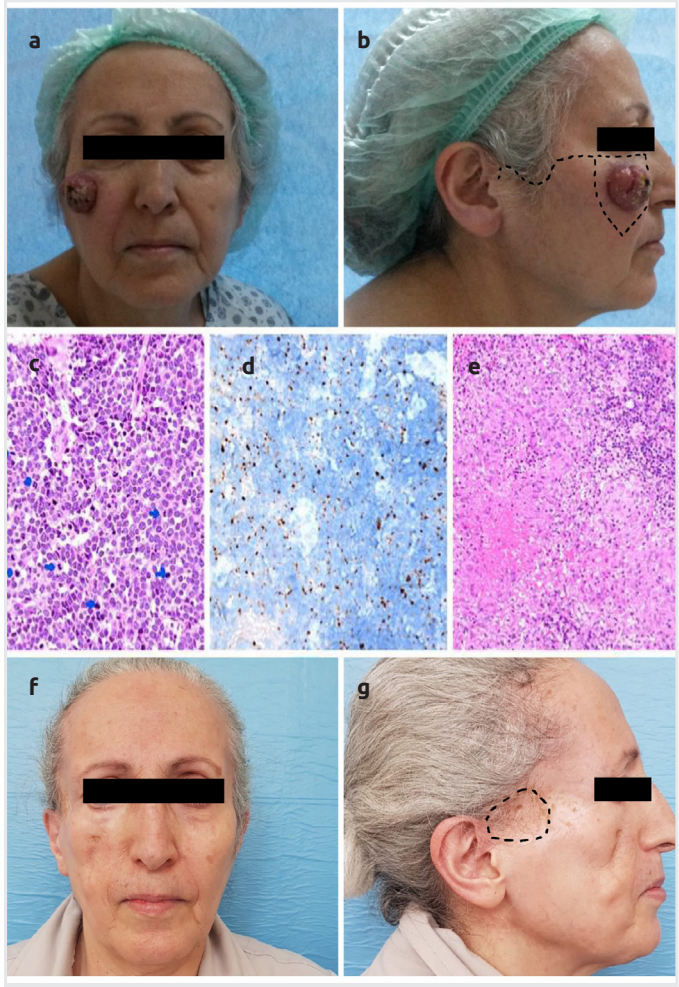

Figure 1 a, b. (upper row). Preoperative frontal and lateral views of the patient. Note the resection borders and the Mustardé flep design on the lateral view

Figure 1 c, d, e, (middle row). c) Merkel Cell Carcinoma: Increased nucleus/cytoplasm ratio in basophilic tumoral cells with dispersed mitotic figures (HE X200:) d) Merkel Cell Carcinoma: Diffuse paranuclear CK20 positivity in tumor cells (x200) e) Necrotizing granulomatous lymphadenitis: Granuloma formation with central necrosis surrounded by epitheloid histiocytes, multinuclear giant cells surrounded by lymphocytes (HE x100)

Figure 1 f, g. Late postoperative frontal and lateral views of the patient. Note the grafted area on the lateral view (lower row)

short period of 1-3 months. The differential diagnosis includes keratoacanthoma, seborrheic keratosis, actinic keratosis, Bowen's disease, squamous cell carcinoma, morpheaform basal cell carcinoma, pyogenic granuloma, nevi, amelanotic melanoma, Kaposi's sarcoma, lymphomas, angiocarcomas, and skin metastases of tumors (8,9).

Merkel cells are dermal sensory neuroendocrine cells which serve as mechanoreceptors in the basal layer of the epidermis. MCCs originate from the dermoepidermal junction. Diagnosis is made with an incisional biopsy (4,8). A small cell blue tumor pattern is seen in the light microscope. These cells have high mitotic activity as it is seen in our case. MCCs are distinguished from other small cell blue tumors such as melanoma, lymphoma, small cell carcinoma, metastatic carcinoid tumor, neuroblastoma and sweat gland tumors by the perinuclear globule staining with low molecular weight cytokeratins such as cytokeratin-20. MCC also reacts to the neuroendocrine markers such as chromagranin, somatophysin, calcitonin and vasoactive intestinal peptide. MCC also reacts to the other neuroendocrine markers such as chromagranin, somatophysin, calcitonin and vasoactive intestinal peptide. MCC is distinguished from the melanoma by negative reaction to S100 and HMB45, from cutaneous metastases of small cell carcinomas by negative reaction to Thyroid transcription factor-1 (T), and from lymphoma by negative reaction to leukocyte common antigen and vimentin (10,11).

The MCCs develop regional metastases in a short period of time. At the time of the diagnosis, 73% of the patients have local lesions, 23% regional lymph node metastasis and 4% distant metastasis. The MCCs often metastasize to the dermis, liver, bones, brain and lymph nodes (3,12). Metastases can be detected by CT, magnetic resonance imaging, PET or octreotide scintigraphy (3).

Wide excision, regional lymph dissection (if there is metastasis) and adjuvant RT can be used in the regional control of the disease. Curative treatment of metastatic MCCs has not been established yet (3,13,14).

While the response rate to cyclophosphamide/adriamycin/vincristine treatment is 75.7%, the response rate to etoposide/cisplatin (EP) is reported to be 55-60% in the case of locally advanced tumor or metastasis in the literature (15). A mortality rate of 3.4% due to the chemotherapy is also reported in the literature. Considering that immunosuppression caused by adjuvant chemotherapy may affect the defense of the patients against the tumor, newly developed immunotherapeutic agents such as avelumab, pembrolizumab, ipilimumab and nivolumab have recently been used (15,16).

The 5-year survival rate varies from 18% to 80% depending on the stage of the MCC disease (17). Therefore, early diagnosis and treatment may improve the survival rates.

Our patient was successfully treated with quadruple anti-TB therapy, 5,400 cGy radiotherapy and chemotherapy (cisplatin and etoposide)." There was no recurrence in the 5-year follow-up. As a result, MCC is a rare, aggressive carcinoma that usually arises in the sun-exposed regions. Physicians should consider MCC in the differential diagnosis when they encounter with a rapidly growing, painless lesion especially in individuals with high ultraviolet exposure and immunosuppression or who are under immunosuppressive therapy. Patients with MCC should be checked up at the short intervals during the first 2 years due to the local recurrences which are frequently seen in this period.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Concept: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Design: S.E.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Data Collection or Processing: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Analysis or Interpretation: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Literature Search: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y., Writing: S.S.E., A.K., O.C.A., Ö.S.K., P.A., P.Y.

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References

1. Amaral T, Leiter U, Garbe C. Merkel cell carcinoma: epidemiology, pathogenesis, diagnosis and therapy. Rev Endocr Metab Disord 2017;18:517-32.
2. Hodgson NC. Merkel cell carcinoma: changing incidence trends. J Surg Oncol 2005;89:1-4.
3. He W, Zhang D, Jiang J, Chen Y, Wu C. Merkel cell carcinoma in the left groin: a case report and review of the literature. Oncol Lett 2015;9:1197-200.
4. Lebbe C, Becker JC, Grob JJ, Malvehy J, Del Marmol V, Pehamberger H, et al. Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. Eur J Cancer 2015;51:2396-403.
5. Hwang W, Kang MS, Kim JW. Two separate nodules of Merkel cell carcinoma occurring concomitantly on one cheek. Arch Craniofac Surg 2019;20:203-6.
6. North VS, Habib LA, Yoon MK. Merkel cell carcinoma of the eyelid: A review. Surv Ophthalmol 2019;64:659-67.
7. Emge DA, Cardones AR. Updates on Merkel Cell Carcinoma. Dermatol Clin 2019;37:489-503.
8. Tai P, Au J. Skin cancer management-updates on Merkel cell carcinoma. Ann Transl Med 2018;6:282.
9. Ogura Y, Enomoto T, Mikami S, Hoshino H, Noda A, Saji O, et al. A rare case of metastasis of Merkel cell carcinoma to the jejunum. J Case Rep 2016;6:378-81.
10. Kuwamoto S. Recent advances in the biology of Merkel cell carcinoma. Hum Pathol 2011;42:1063-77.

11. Taşkın B. Merkel Cell Carcinoma. Güncel Dermatoloji Dergisi 2017;2:69-71.

12. Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol 2001;8:204-8.

13. Howell RS, Rice JA, Sticco K, Donovan V, Castellano M, Gillette B, et al. An unusual presentation of Merkel cell carcinoma: a case report. J Surg Case Rep 2018;8:rjy185.

14. Green MD, Hayman JA. Radiotherapy in the Multidisciplinary Management of Merkel Cell Carcinoma. J Natl Compr Canc Netw 2018;16:776-81.

15. Tai PT, Yu E, Winquist E, Hammond A, Stitt L, Tonita J, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. J Clin Oncol 2000;18:2493-9.

16. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374-85.

17. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol 2008;58:375-81.

Review

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Palliative Care and Phytotherapy in Patients with Cancer

Kanser Hastalarında Palyatif Bakım ve Fitoterapi

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ABSTRACT

Cancer is defined as a complex disease that occurs with the uncontrolled proliferation of cells and develops under the influence of genetic and environmental conditions. Chemotherapy and radiotherapy are frequently used in cancer treatment. Side effects related to these treatments are observed in most of the patients. Palliative care, which is an important part of cancer management today, aims to alleviate the symptoms and side effects of these treatments and to increase the quality of life of the patient. A growing number of patients with cancer are inclined towards complementary and integrative medicine, including herbal medicine. The interest in this field is increasing because it has been shown by preclinical and clinical studies that some phytotherapeutic products can reduce the side effects of chemotherapy and radiotherapy. This review summarizes phytotherapeutic approaches supported by clinical studies for palliative care in cancer patients.

Keywords: Palliative, cancer, phytotherapy

ÖZ

Kanser, hücrelerin kontrolsüz çoğalması ile ortaya çıkan, genetik ve çevresel koşulların etkisi altında gelişen kompleks bir hastalık olarak tanımlanmaktadır. Kemoterapi ve radyoterapi kanser tedavisinde sıklıkla kullanılmakta ve hastaların çoğunda buna bağlı yan etkiler gözlenmektedir. Günümüzde kanser yönetiminin önemli bir parçası olan palyatif bakım da bu tedavilerde ortaya çıkan semptomların ve yan etkilerin hafifletilmesini sağlayıp hastanın yaşam kalitesini artırmayı hedeflemektedir. Giderek artan sayıdaki kanser hastası, bitkisel ilaçlar da dahil olmak üzere tamamlayıcı ve entegratif tıbba yönelmiş durumdadır. Bazı fitoterapötik ürünlerin kemoterapi ve radyoterapiye bağlı yan etkileri azaltabildiğinin preklinik ve klinik çalışmalarda gösterilmesi sebebiyle bu alana olan ilgi artmaktadır. Bu derleme kanser hastalarında uygulanabilecek palyatif bakımda, klinik çalışmalarla desteklenen fitoterapötik yaklaşımları özetlemektedir.

Anahtar Sözcükler: Palyatif, kanser, fitoterapi

Introduction

Although more people are diagnosed as having cancer today, the life expectancy of patients is increasing with the increase of studies on cancer. Chemotherapy and radiotherapy are effective and comprehensive approaches in cancer management. However, the frequent occurrence of side effects such as oral mucositis, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, hematopoietic system damage, cardiotoxicity and neurotoxicity limits the clinical use of chemotherapy and radiotherapy (1,2). However, fatigue is a common problem in patients with cancer (3). Therefore, palliative care, which is one of the strategies to reduce the side effects of chemotherapy and radiotherapy, may be important for these patients. Especially patients with terminal stage cancer often need palliative care. Pressure ulcers are also common in patients who need palliative care, and conventional therapies are often insufficient (4).

In a study conducted on cancer patients, it was shown that 62% of patients used complementary therapies. It was stated that 82% of these patients used at least one herbal product and 30% used herbal products together with chemotherapy drugs (5).

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The purpose of applying palliative care with phytotherapy is to reduce the frequency of symptoms that occur as a result of life-threatening diseases and, as a result, to improve the quality of life. In this review, we will talk about phytotherapeutic approaches supported by clinical studies to increase the quality of life of the person against cancer itself or against the negative conditions that arise as a result of the treatment applied.

The Use of Phytotherapy in Oral Mucositis

Oral mucositis is a common complication that starts with oxidative stress and inflammation and is seen in patients receiving chemotherapy and radiotherapy (6). In addition to disrupting oral nutrition, it also exposes the mucosa to contamination due to disruption of the mucosal barrier against microbial agents and may lead to systemic bacteremia, fungemia and viremia (7).

Severe stomatitis results in discontinuation of cancer chemotherapeutics and an increased risk of local and systemic infections. *Chamomile* (*Matricaria recutita*) is widely used for its antioxidant, antimicrobial and anti-inflammatory effects. Due to these properties, it is considered to be a useful option in cases such as oral mucositis or recurrent aphthous stomatitis. According to a randomized clinical trial in which 36 patients with recurrent aphthous stomatitis were included, it was reported that a significant reduction in pain and burning sensation was achieved in the group using chamomile mouthwash (Matrica Drop®, Barij Essence Co.) containing 0.09-0.17 mg of kamazulene per milliliter compared to placebo. As a result of this study, it was stated that chamomile mouthwash treats pain and burning sensation without any side effects, and can be used safely in patients with recurrent aphthous stomatitis (8).

Aloe vera gel has been used in dermatological ailments for centuries due to its wound healing and antibacterial effects. According to a randomized controlled clinical study conducted by Mansouri et al. (9) on 64 patients with Acute lymphoid leukemia and Acute myeloid leukemia, it was stated that the severity and degree of pain of stomatitis were significantly reduced in the aloe vera mouthwash group compared to the control group. Therefore, the authors recommend the use of solutions containing aloe vera gel in patients receiving chemotherapy to improve nutritional status and maintain oral hygiene.

Turmeric (*Curcuma longa rhizome*) is a spice and herb that is known to have many health benefits and has traditional uses. Recent pharmacological studies have shown that curcumin in turmeric has strong antioxidant, antimicrobial, anti-inflammatory and anticancer activities (10). According to a study conducted in 20 patients with cancer who received chemotherapy and radiotherapy, the patients were randomly divided into two, one group was given the standard preventive oral care, 0.2% chlorhexidine mouthwash, while the other group was given a freshly prepared 0.004% curcumin mouthwash. Patients were expected to gargle three times a day for 20 days. It was reported that rapid wound healing was achieved in the group receiving curcumin mouthwash and it was better than chlorhexidine mouthwash in terms of patient compliance in the treatment of radiotherapy-chemotherapy-induced oral mucositis (11).

Black mulberry molasses is a traditionally widely used food ingredient in the treatment of mucositis in Turkey. Recently, a randomized controlled clinical trial was published in which 80 patients with head and neck cancer undergoing radiotherapy who used black mulberry molasses were included (12). As a result of this study, it was stated that the use of black mulberry molasses together with radiotherapy might be an effective treatment for the prevention of radiation-induced mucositis in patients with head and neck cancer (12).

Propolis is a natural product rich in flavonoids and known for its antiulcer, antibacterial, antifungal and anti-inflammatory effects (13). Studies have been reported showing that the use of water-based propolis extract as a mouthwash (14,15) effectively treats chemotherapy and radiotherapy-induced oral mucositis in patients with head and neck cancer and in patients with leukemia (16,17). On the other hand, according to the results of a double-blind, randomized, placebo-controlled study, it was stated that propolis was not recommended for severe oral mucositis in pediatric patients (18).

Calendula [(*Calendula officinalis*) (*C. officinalis*)] has long been used in traditional medicine and since 2008 has been recognized as an herbal medicinal product by the European Medicines Agency. Both the flowers and leaves of the calendula are used in folk medicine today as an anti-inflammatory and antispasmodic drug, in the treatment of minor burns, bruises and rashes. It is also used in alleviating the discomfort caused by gastric ulcer, oral and pharyngeal mucosa inflammation (19).

In a randomized controlled clinical study involving 40 patients with head and neck cancer who received radiotherapy, the effectiveness of mouthwash containing 2% ethanolic flower extract of *C. officinalis* on oropharyngeal mucositis was evaluated. It was concluded that *C. officinalis* was effective in reducing the density of oral mucositis, but could not completely prevent its formation (20).

Radiodermatitis and Phytotherapy

Radiodermatitis is defined as a skin lesion caused by excessive exposure to ionizing radiation, which can lead to dehydration of the skin and serious complications (ulceration, local infection). In patients with breast cancer and head and neck cancer, the skin area in the treatment area is more sensitive and has more skin folds. Therefore, it is a major risk factor for the development of radiodermatitis.

According to a randomized double-blind controlled clinical study evaluating the efficacy of *C. officinalis* on radiodermatitis and head and neck cancer, a lotion prepared with 4% *C. officinalis oil* (olive oil maceration) was applied to one group, while the other group was treated with a lotion rich in essential fatty acids (EFA). The incidence of grade 1 dermatitis was 40.73% in the EFA group and 25% in the *C. officinalis* group. In addition, after the last radiotherapy session, the incidence of grade 2 or 3 radiodermatitis was 21.43% in the *C. officinalis* group, while this rate nearly doubled in the EFA group (46.16%). According to the results of this study, it was reported that *C.officinalis* was effective in the prevention and treatment of radiodermatitis (21).

There is a randomized, double-blind, phase III, clinical study examining the efficacy of *C. officinalis* on breast cancer after radiotherapy. This study evaluated the efficacy of grade 2 or higher radiation-induced acute dermatitis on 254 patients with breast cancer (22). When the *C. officinalis* oil-containing cream applied group was compared with the trolamine-administered group, it was stated that grade 2 and higher acute dermatitis formation was significantly lower in the *C. officinalis* group. In addition, it was reported that patients receiving *C. officinalis* had less interruption of radiotherapy and no allergic reaction, and *C. officinalis* significantly reduced radiation-induced pain. Therefore, it has been emphasized that *C officinalis* oil may be a good non-steroidal agent for the prevention of radiation-induced dermatitis in patients with breast cancer (22). In addition, a recent meta-analysis indicated that trolamine was ineffective in the prevention and treatment of radiation dermatitis (22). Therefore, the efficacy of *C. officinalis* here needs to be supported by other clinical studies.

Aloe vera gel is widely used in the treatment of radiation dermatitis. The part of the plant used topically is a clear, viscous gel-like structure that appears when the leaves of the plant are cut. A study on 60 patients with cancer (breast, head and neck, pelvis cancer) evaluated the effectiveness of aloe vera gel on radiodermatitis. Patients were asked to apply aloe vera lotion to half of the radiotherapy application area. No lotion was applied to the other half. The lotion contained aloe vera as well as lanolin oil, glyceryl stearate, collagen, tocopherol, allantoin and paraben. The lotion containing aloe vera gel was applied to one side of the radiotherapy treated area for 6 weeks. It was reported that from the 4th week to the end of the evaluation period, the decrease in the degree of dermatitis on the side where aloe vera gel was applied was statistically significant, and the highest statistical difference was seen in the 5th and 6th weeks of radiotherapy, when the patients received high radiation dose (23).

The Use of Phytotherapy against Cancer-Associated Fatigue

Cancer-related fatigue (CRF) is one of the most common symptoms that occurs during cancer treatment. Fatigue complaints are frequently reported in 80% to 96% of patients receiving chemotherapy and 60% to 93% of patients receiving radiotherapy (24). CRF is a different condition from fatigue caused by excessive physical activity or flu-related fatigue. In cases of CRF, fatigue occurs during normal activities and becomes pathological and seriously affects the patient's quality of life (25). Although the underlying mechanism of CRF is not fully understood, factors such as proinflammatory cytokine network, dysfunction in the hypothalamo-pituitary adrenal axis, circadian rhythm disruption, and mitochondria dysfunction are thought to cause CRF (26,27).

Ginseng is an herb that has been used in Asian countries for thousands of years. There are 2 main types of ginseng: *Asian/ Korean ginseng* [(*Panax ginseng*) (*P. ginseng*)] and *American ginseng* (*Panax quinquefolius*). Both types have similar ingredients. *P. ginseng* is the most studied species in terms of its antioxidant, anticancer, and anti-inflammatory properties (28).

According to a study of quality of life in patients with cancer conducted by Kim et al. (29), patients were observed for 12 weeks and the effectiveness of 3000 mg *P. ginseng* daily over placebo was compared. It was reported that there was a significant improvement in mental and physical functionality in the group given *P. ginseng* compared to the placebo. It was stated that the improvement in quality of life might occur as a result of the anxiolytic effect of ginsenosides by binding to gamma aminobutyric acid receptors (30).

In a randomized double-blind multicenter study conducted by Barton et al. (31), the effectiveness of American ginseng on CRF was investigated. Patients who were diagnosed as having cancer in the last two years and received or completed treatment were included in the study. The effects of 2,000 mg of *Panax quinquefolius* containing 3% ginsenoside on CRF were compared against placebo. As a result of 8 weeks of observation, it was reported that the fatigue scoring in 2,000 mg of *Panax quinquefolius* daily group was found to be significantly lower compared to placebo.

Rhodiola Rosea (*Golden root*) roots have been used for centuries as an "adaptogen" to enhance physical and mental performance and combat stress (32,33). Currently, *Rhodiola rosea* (*R. rosea)* extracts are used as dietary supplements in Europe, Asia and the United States for similar indications (34).

R. rosea roots have different effects on the central nervous system depending on the dose. While larger doses have a sedative effect, smaller doses increase the release of monoamines and activate the cerebral cortex and limbic system (35). With *in vivo* studies, it was predicted that *R. rosea* roots could increase the effect of chemotherapy in general and potentially reduce side effects such as fatigue and cognitive impairment (36).

Although there is no direct study of *R. rosea* on CRF, there are several clinical studies evaluating the effectiveness of *R. rosea* in mental and physical fatigue. According to a randomized, double-blind clinical study on stress-induced fatigue conducted by Panossian et al. (37), it was reported that standardized root extracts of *R. rosea* reduced the stress-induced cortisol response and had a significant effect on fatigue levels compared with placebo. *Guarana* (*Paullinia cupana*) is a plant of Brazilian origin. In two randomized, placebo-controlled studies, the positive effects of using guarana extract at doses of 75 mg per day (containing 11-12 mg of caffeine) on memory and cognitive function were reported (38,39). According to a randomized double-blind pilot study evaluating its efficacy on CRF and depression due to its stimulant effects, it was stated that no significant result could be achieved on CRF in the group given 75 mg guarana extract daily compared to placebo (40). In a study that included 77 patients with breast cancer receiving chemotherapy and used a higher dose of guarana compared to the previous study, the effectiveness of guarana on fatigue, anxiety and depression was investigated. As a result of the study, it was stated that guarana was an effective, non-toxic, inexpensive and effective herbal product and had a positive effect on fatigue in patients with breast cancer receiving chemotherapy (41).

Phytotherapy for Wound Healing

Wound formation, which is frequently encountered in patients in palliative care, is an important problem that threatens life and reduces the quality of life. It is stated that wound formation occurs in 35% of palliative care patients (4). These wounds include pressure ulcers, venous or arterial leg ulcers, diabetic ulcers, and malignant fungating ulcers (42).

Aloe vera gel is a widely used plant due to its antibacterial, antiviral, and anti-inflammatory effects (43-45). It has been reported that aloe vera gel is more successful in chronic wounds than in acute wounds (46). In previous studies, aloe vera gel preparations have been reported to have wound-healing properties by increasing macrophage and fibroblast activity (46,47). Aloe vera can inhibit the inflammatory process by reducing leukocyte adhesion and limiting the activity of proinflammatory cytokines such as tumor necrosis factor-α and Interleukin-6 (48). Thanks to the glucomannan in the aloe vera gel content, it increases the production of collagen by stimulating the Fibroblast growth factor. Aloe vera contributes to wound healing not only by increasing collagen production at the wound site, but also by increasing collagen cross-links, providing tissue integrity thanks to the amino acids and minerals such as zinc in its content (47,48).

There is a case report in which a patient with a 30x10 cm ulcer in the pretibial region was treated with surgical debridement and antibiotic therapy, and after 160 days, there was no response to the treatment, and aloe vera gel was applied. The mucilage structure in the aloe vera leaves was collected and mixed with a preservative and lubricant and applied to the ulcerated area. It was reported that with the tissue healing at the end of the 58th day, a decrease in pain, exudate and erythematous tissue was achieved (47).

It was reported that aloe vera gel reduced the healing time to 9 days in first and second degree burns (49). It is stated that once or twice a day aloe vera gel dressing may be a more effective method than existing treatments (vaseline dressing, silver sulfadiazine 1% ointment and framycetin cream). In this way, it allows to reduce the healing time, to prevent infection in the wound area, and to relieve redness and itching (49).

According to a randomized double-blind controlled trial using a cream formulation containing aloe vera gel and olive oil, and including 61 patients with chronic wounds (41 pressure ulcers, 13 diabetic wounds, and 6 venous ulcers), patients were randomly divided into two and treated with phenytoin. It was reported that the cream containing aloe vera gel and olive oil significantly accelerated the biological healing of chronic wounds and helped to reduce the severity of pain with a higher efficacy than the cream containing phenytoin (50).

C. officinalis flower extracts can be used in inflammatory conditions of the skin such as herpes, sunburns and dermatitis. An observational study of 41 patients with pressure ulcers for more than 3 months evaluated wound healing after spray application of *C. officinalis* flower extract to patients. It was stated that the wound healing rates at 15 and 30 weeks were 63% and 83%, respectively, and the spray containing *C. officinalis* flower extract increased wound healing (51).

St. John's Wort (Hyperium perfaratum) is widely grown in our country and there are 84 species in our country. Topical formulations such as oily extracts or ointments prepared with the blooming aerial parts of *St. John's Wort* have been used in the treatment of a wide variety of dermatological problems such as superficial wounds and burns, bruises, contusions. According to the case report of an 83-year-old patient with a pressure ulcer followed in the intensive care unit, the extract obtained from *St. John's Wort* maceration was applied to the patient twice a day for 40 days, and the follow-up was ensured. Macroscopic evaluation of wound size and stages and histopathological examinations were performed. The authors stated that as a result of macroscopic and histopathological examinations, oily maceration of *St. John's Wort* provided significant efficacy in the treatment of pressure ulcers (52).

In another study conducted on 30 patients with bedsores, in addition to routine wound care, half of the patients were treated with *St. John's Wort* oil, while only olive oil was applied to the other half. It was reported that the wound area and wound depth were significantly reduced in the St. John's Wort oil applied group compared to the control group (15).

Conclusion and Recommendations

Applying palliative treatment in patients with cancer is very important in order to improve the social and physical condition of the patient, as well as to increase the quality of life. Side effects that may occur due to the disease itself or the drugs used for its treatment can reduce the quality of life of the patient. Therefore, approaches that can prevent or reduce these side effects are very important.

CRF is one of the most common complaints in patients with cancer. *P. ginseng* is the most researched plant species in this field. In addition to the use of adaptogen plants in CRF, regular nutrition, stress management and regular exercise can be added to the treatment plan of patients.

Radiodermatitis and oral mucositis observed in palliative care patients receiving radiotherapy or chemotherapy are complaints that may affect the patient's continuity of treatment. *C. officinalis* is a plant that is used in both radiodermatitis and oral mucositis. It should be noted that topical formulations containing the standardized extract of this plant can be a complementary treatment option in addition to existing treatments in reducing complaints due to chemotherapy or radiotherapy. Indications for chamomile approved by Commission E include inflammation of the mouth and pharynx. For external use, it is recommended to prepare an infusion of 2 teaspoons of chamomile with 2 glasses of water (14). For the same indication, it is recommended to prepare 1-2 g of powdered herb for *C. officinalis* as an infusion in a glass of water (14). Since there are easily accessible plants in our country, the preparation of solutions of infusions prepared from these plants to ensure oral hygiene in the treatment of oral mucositis can be considered as an auxiliary option for treatment.

Another problem frequently encountered in palliative care patients is wound formation, especially pressure ulcers. Aloe vera gel and St. John's Wort oil are the herbal products with

the most research in wound treatment. John's wort oil, which is obtained from St. John's Wort and widely grown in Anatolia, has a traditional use in wound healing and its effectiveness has been supported by clinical studies. For this reason, it can make a positive contribution to wound healing by adding it to the existing treatment in palliative care patients.

As seen in the clinical studies mentioned in our review, symptom-oriented use of phytotherapeutic products in palliative care patients can be considered a rational approach. Phytotherapeutic products have high antioxidant capacity due to the bioactive substances in their content. While this may provide support to palliative care patients, it may also cause a decrease in the effectiveness of chemotherapeutics in the chemotherapy group. Although antioxidants are a useful option for the harmful effects caused by chemotherapeutics, their simultaneous use may reduce the therapeutic effect of the anticancer drugs used. For this reason, physician and pharmacist consultation is required for the prophylactic and therapeutic use of phytotherapeutics, which have been used for many years.

Ethics

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Authorship Contributions

Concept: M.N.A., A.A., M.K., Design: M.N.A., A.A., Data Collection or Processing: M.N.A., Analysis or Interpretation: M.N.A., A.A., M.K., Literature Search: M.N.A., Writing: M.N.A.

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References

1. Turcotte LM, Liu Q, Yasui Y, Arnold MA, Hammond S, Howell RM, et al. Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015. JAMA 2017;317:814.
2. Shapiro CL. Highlights of Recent Findings on Quality-of-Life Management for Patients With Cancer and Their Survivors. JAMA Oncol 2016;2:1401-2.
3. Bag B. Fatigue Related Psychosocial Problems in Cancer Patients and their Solutions. Archives Medical Review Journal 2012;21:253-73.
4. Tippett AW. Palliative wound treatment promotes healing in hospice. Clinical Nursing Studies. 20158;3.
5. Kucukoner M, Bilge Z, Isıkdogan A, Ali Kaplan M, Inal A, Urakci Z. Complementary and Alternative Medicine Usage in Cancer Patients in Southeast of Turkey. Afr J Tradit Complement Altern Med 2012;10:21-5.
6. Zhang QY, Wang FX, Jia KK, Kong LD. Natural Product Interventions for Chemotherapy and Radiotherapy-Induced Side Effects. Front Pharmacol 2018;9:1253.
7. Kiki İ. Kemoterapiye Bağlı Mukozit. Atatürk Üniversitesi Diş Hekimliği Fakültesi Dergisi, 2014; 24: 158-161.
8. Seyyedi SA, Sanatkhani M, Pakfetrat A, Olyaee P. The therapeutic effects of chamomilla tincture mouthwash on oral aphthae: A Randomized Clinical Trial. J Clin Exp Dent 2014;6:e535-8.
9. Mansouri P, Haghighi M, Beheshtipour N, Ramzi M. The Effect of Aloe Vera Solution on Chemotherapy-Induced Stomatitis in Clients with Lymphoma and Leukemia: A Randomized Controlled Clinical Trial. Int J Community Based Nurs Midwifery 2016;4:119-26.
10. Liu Z, Huang P, Law S, Tian H, Leung W, Xu C. Preventive effect of Curcumin against chemotherapy-induced side-effects. Front Pharmacol 2018;9:1374.
11. Patil, K, Guledgud M, Kulkarni PK, Keshari D, Tayal S. Use of curcumin mouthrinse in radio-chemotherapy induced oral mucositis patients: a pilot study. Journal of clinical and diagnostic research, 2015; 9: ZC59-ZC62.
12. Demir Doğan M, Can G, Meral R. Effectiveness of Black Mulberry Molasses in Prevention of Radiotherapy-Induced Oral Mucositis: A Randomized Controlled Study in Head and Neck Cancer Patients. J Altern Complement Med 2017;23:971-9.
13. Dodwad V, Kukreja BJ. Propolis mouthwash: A new beginning. J Indian Soc Periodontol 2011;15:121-5.
14. Company ME. PDR for Herbal Medicine: Physicians' Desk Reference for Herbal Medicines Thomson PDR. 2004.
15. Wölfle U, Seelinger G, Schempp CM. Topical application of St. John's wort (Hypericum perforatum). Planta Med 2014;80:109-20.
16. Javadzadeh Bolouri A, Pakfetrat A, Tonkaboni A, Aledavood SA, Fathi Najafi M, Delavarian Z, et al. Preventing and Therapeutic Effect of Propolis in Radiotherapy Induced Mucositis of Head and Neck Cancers: A Triple-Blind, Randomized, Placebo-Controlled Trial. Iran J Cancer Prev 2015;8:e4019.
17. Eslami H, Pouralibaba F, Falsafi P, Bohluli S, Najati B, Negahdari R, et al. Efficacy of Hypozalix spray and propolis mouthwash for prevention of chemotherapy-induced oral mucositis in leukemic patients: A double-blind randomized clinical trial. J Dent Res Dent Clin Dent Prospects 2016;10:226-33.
18. Tomaževič T, Jazbec J. A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. Complement Ther Med 2013;21:306-12.
19. Mentha D, Rastogi P, Kumar A, Chaudhary AK. MEHTA, Devansh, et al. Review on pharmacological update: Calendula officinalis Linn. Inventi Impact: Planta Activa, 2012; 4:195-203.
20. Babaee N, Moslemi D, Khalilpour M, Vejdani F, Moghadamnia Y, Bijani A, et al. Antioxidant capacity of calendula officinalis flowers extract and prevention of radiation induced oropharyngeal mucositis in patients with head and neck cancers: a randomized controlled clinical study. Daru 2013;21:18.
21. Schneider F, Danski MTR, Vayego SA. [Usage of Calendula officinalis in the prevention and treatment of radiodermatitis: a randomized double-blind controlled clinical trial]. Rev Esc Enferm USP 2015;49:221-8.

22. Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X. Phase III Randomized Trial of Calendula Officinalis Compared With Trolamine for the Prevention of Acute Dermatitis During Irradiation for Breast Cancer. J Clin Oncol 2004;22:1447-53.
23. Haddad P, Amouzgar-Hashemi F, Samsami S, Chinichian S, Oghabian MA. Aloe vera for prevention of radiation-induced dermatitis: a self-controlled clinical trial. Curr Oncol 2013;20:e345-8.
24. Stasi R, Abriani L, Beccaglia P, Terzoli E, Amadori S. Cancer-related fatigue. Cancer 2003;98:1786-801.
25. Aschuler L. Natural Interventions for Posttreatment Cancer-related Fatigue. Natural Medicine Journal. cited 25 Jan 2022. Avalible from: https://www.naturalmedicinejournal.com/journal/natural-interventions-posttreatment-cancer-related-fatigue
26. Collado-Hidalgo A, Bower JE, Ganz PA, Irwin MR, Cole SW. Cytokine gene polymorphisms and fatigue in breast cancer survivors: Early findings. Brain Behav Immun 2008;22:1197-200.
27. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and Behavioral Symptoms After Breast Cancer Treatment: Do Fatigue, Depression, and Sleep Disturbance Share a Common Underlying Mechanism? J Clin Oncol 2011;29:3517-22.
28. Kiefer D, Pantuso T. Panax ginseng. American Family Physician. 2003;68:1539-1542
29. Kim JH, Park CY, Lee SJ. Effects of sun ginseng on subjective quality of life in cancer patients: a double-blind, placebo-controlled pilot trial. J Clin Pharm Ther 2006;31:331-4.
30. Park JH, Cha HY, Seo JJ, Hong JT, Han K, Oh KW. Anxiolytic-like effects of ginseng in the elevated plus-maze model: Comparison of red ginseng and sun ginseng 2005;29:895-900.
31. Barton DL, Liu H, Dakhil SR, Linquist B, Sloan JA, Nichols CR, et al. Wisconsin Ginseng (Panax quinquefolius) to Improve Cancer-Related Fatigue: A Randomized, Double-Blind Trial, N07C2. J Natl Cancer Inst 2013;105:1230-8.
32. Kotecha R, Takami A, Espinoza JL. Dietary phytochemicals and cancer chemoprevention: a review of the clinical evidence. Oncotarget 2016;7:52517-29.
33. Panossian A, Wikman G, Sarris J. Rosenroot (Rhodiola rosea): Traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine 2010;17:481-93.
34. Booker A, Jalil B, Frommenwiler D, Reich E, Zhai L, Kulic Z, et al. The authenticity and quality of Rhodiola rosea products. Phytomedicine 2016;23:754-62.
35. Busia, K. Fundamentals of Herbal Medicine: Major Plant Families, Analytical Methods, Materia Medica. Xlibris Corporation, 2016.
36. Brown RP, Gerbarg PL, Ramazanov Z. Rhodiola rosea: A Phytomedicinal Overview. American Botanical Council. BROWN, Richard P., et al. Rhodiola rosea. A phytomedicinal overview. 2002;56:40-52.
37. Panossian A, Hovhannisyan A, Abrahamyan H, Gabrielyan E, Wikman G. Pharmacokinetic and pharmacodynamic study of interaction of Rhodiola rosea SHR-5 extract with warfarin and theophylline in rats. Phytother Res 2009;23:351-7.
38. Haskell CF, Kennedy DO, Wesnes KA, Milne AL, Scholey AB. A double-blind, placebo-controlled, multi-dose evaluation of the acute behavioural effects of guaraná in humans. J Psychopharmacol 2007;21:65-70.
39. Kennedy DO, Haskell CF, Wesnes KA, Scholey AB. Improved cognitive performance in human volunteers following administration of guarana (Paullinia cupana) extract: comparison and interaction with Panax ginseng. Pharmacol Biochem Behav 2004;79:401-11.
40. da Costa Miranda V, Trufelli DC, Santos J, Campos MP, Nobuo M, da Costa Miranda M, et al. Effectiveness of guaraná (Paullinia cupana) for postradiation fatigue and depression: Results of a pilot double-blind randomized study. J Altern Complement Med 2009;15:431-3.
41. de Oliveira Campos MP, Riechelmann R, Martins LC, Hassan BJ, Casa FBA, del Giglio A. Guarana (Paullinia cupana) improves fatigue in breast cancer patients undergoing systemic chemotherapy. J Altern Complement Med 2011;17:505-12.
42. Chrisman CA. Care of chronic wounds in palliative care and end-of-life patients. Int Wound J 2010;7:214-35.
43. Shelton RM. Aloe Vera: Its Chemical and Therapeutic Properties. Int J Dermatol 1991;30:679-83.
44. Ahmad S, Hassan A, Abbasi WM, Rehman T. Phytochemistry and pharmacological potential of Cassia absus - a review. J Pharm Pharmacol 2018;70:27-41.
45. Reddy CU, Reddy KS, Reddy JJ. Aloe vera - a wound healer. Asian Journal of Oral Health & Allied Sciences 2011;1:91-2.
46. Hekmatpou D, Mehrabi F, Rahzani K, Aminiyan A. The Effect of Aloe Vera Clinical Trials on Prevention and Healing of Skin Wound: A Systematic Review. Iran J Med Sci 2019;44:1-9.
47. Avijgan M. Phytotherapy: an alternative treatment for non-healing ulcers. J Wound Care. 2004;13:157-8.
48. Duansak D, Somboonwong J, Patumraj S. Effects of Aloe vera on leukocyte adhesion and TNF-alpha and IL-6 levels in burn wounded rats. Clin Hemorheol Microcirc 2003;29:239-46.
49. Hekmatpou D, Mehrabi F, Rahzani K, Aminiyan A. The Effect of Aloe Vera Clinical Trials on Prevention and Healing of Skin Wound: A Systematic Review. Iran J Med Sci 2019;44:1-9.
50. Panahi Y, Izadi M, Sayyadi N, Rezaee R, Jonaidi-Jafari N, Beiraghdar F, et al. Comparative trial of Aloe vera/ olive oil combination cream versus phenytoin cream in the treatment of chronic wounds. J Wound Care 2015;24:459-65.
51. Buzzi M, Freitas F de, Winter M de B. Cicatrização de úlceras por pressão com extrato Plenusdermax® de Calendula officinalis L. Rev Bras Enferm 2016;69:250-7.
52. Yücel A, Kan Y, Yesilada E, Akın O. Effect of St.John's wort (Hypericum perforatum) oily extract for the care and treatment of pressure sores; a case report. J Ethnopharmacol 2017;196:236-41.