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# EDITORIAL

**Dear Readers;**

We are very happy to be together once again with a new issue and new topics. While we were experiencing normalization at the end of the Covid pandemic, we experienced difficult times again with the "Kahramanmaraş Earthquake", which was defined as the disaster of the century in our country. Our country, as a single heart, started to leave this problem behind by joining hands. Bezmialem Vakıf University also fulfilled its responsibilities in the process in which many health workers and physicians lost their lives. During this period when wounds were healed, our university provided support both in education and health. We would like to thank our senior management and the members of our university who provided this opportunity.

In this issue, you can find many interesting and valuable articles. We chose the cover art from the study of Gürses M et al. We are pleased that many articles in the field of dentistry have been sent to our journal recently. We present the authors' article titled "Clinical Evaluation of Class II Restorations Made with Bulk-fill Restorative Materials" for the information of interested friends. Other studies are "Microhardness, Degree of Conversion, and Water Sorption/Solubility of Non-expired and Expired (Two and Three Years) Dental Composites" by DÜLGER K et al., "The Role of Clinical and Inflammatory Parameters to Predict the Success of Medical Treatment in Patients with Tubo-ovarian Abscess" by AKTOZ F et al., "Cerebroplacental Ratio During the Third Trimester of Pregnancy: A Prospective Case-Control Study" by KIRLANGIÇ MM et al., and "Aromatherapy in Cancer Patients Receiving Palliative Care" by EGELİ D et al.

I would like to point out that the study of EGELİ D et al. titled "Aromatherapy in Cancer Patients Receiving Palliative Care" is also interesting. I hope you will find this article interesting, which looks at the symptomatic treatment of palliative care patients, which is needed more and more every day in our age, from a different perspective.

Again, intensive labor was spent for this issue. We would like to thank our dean's office for helping us overcome the difficulties experienced in the selection of referees by identifying the department editors. We would like to welcome these friends, whose names we will share with you as of the next issue.

I would like to thank you, our esteemed readers, authors and referees, on behalf of myself and our editorial board. Hope to meet you in the next issue.

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

Commentary

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# Does Vitamin D Prevent Cancer?

## D Vitamini Kanseri Önler mi?

Adem AKÇAKAYA

Bezmialem Vakıf University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

**Dear Readers,**

The relationship between vitamin D and cancer has been discussed for a long time. Recently, it has become popular again with the increase in its use during the coronavirus disease period and the acceptance of its protective effect from infection. In addition to its different uses, many studies have been conducted on its cancer-protective effect, the need for vitamin D in patients with cancer and the ways of obtaining it. As a surgeon dealing with cancer surgery, I evaluated this patient group with a new perspective as a result of my clinical observations and came to the conclusion that vitamin D levels should definitely be evaluated in these patients.

Vitamin D is a fat-soluble vitamin obtainable from the diet, as well as a seco-steroidal prohormone produced in the skin by ultraviolet B (UVB, 290-320 nm) from sunlight. Vitamin D undergoes two-step processing in the liver and kidney to synthesize calcitriol, a biologically active form that binds to the vitamin D receptor (VDR) to activate its various physiological functions (1,2). There are 2 main isoforms of vitamin D; Vitamins D2 and D3 (3,4). Dietary or skin-derived vitamin D binds to the circulating vitamin D binding protein (VDBP) and is first delivered to the liver. In the liver, vitamin D is metabolized to 25(OH)D (calcidiol) by vitamin D 25-hydroxylase (CYP2R1 and CYP27A1), the major circulating form of vitamin D in serum (5,6).

The classic role of vitamin D is to regulate calcium and phosphate metabolisms, which are essential for bone remodeling. However, extensive studies in recent years have suggested that low sunlight exposure and vitamin D deficiency are also associated with an increased risk of many other non-skeletal diseases such as cancer (7-10).

The first observation of an inverse correlation between sunlight exposure and overall cancer incidence and mortality in North America was published about 80 years ago (11). Then, in 1980 and 1992, the first epidemiological studies were reported linking low sunlight exposure with a high risk of colon cancer and prostate cancer, respectively. It has been suggested that, rather than exposure to sunlight, vitamin D may protect against the risk of development of colon cancer and prostate cancer (12,13). Since then, many epidemiological studies have supported and expanded the UVB-vitamin D-cancer hypothesis in 18 different cancer types (14). The hypothesis has further been supported by studies showing a direct relationship between vitamin D and cancer risk. Several population-based studies have demonstrated an inverse correlation between serum 25-hydroxyvitamin D (25(OH)D) levels and increased risk of colon (15), breast (16), prostate (17), gastric and other cancers. Therefore, it is stated that vitamin D deficiency may contribute to the development and progression of many types of cancer, and therefore, maintaining adequate serum vitamin D levels may be beneficial for the prevention and treatment of cancer. The clinical use of calcitriol or vitamin D analogues has been investigated, as numerous epidemiological and experimental data have demonstrated the beneficial role of vitamin D in the prevention and treatment of various types of cancer (18).

### Anticancer Properties of Vitamin D

Since the beneficial effects of vitamin D in preventing and treating cancer have been observed in epidemiological and preclinical studies, several mechanisms have been proposed to explain its anticancer effects. Data in the literature show that vitamin D can regulate the entire tumorigenesis process, from onset to metastasis and cell-microenvironment interactions (18). These mechanisms include regulation of cell behaviors such as proliferation, differentiation, apoptosis, autophagy and epithelial-mesenchymal transition and modulation of cell-microenvironment interactions such as angiogenesis, antioxidants, inflammation and the immune system.

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The most important extraskeletal function of vitamin D is its role in the modulation of the immune system (19,20). This includes supporting innate immune system cells such as monocytes, macrophages and dendritic cells in their fight against bacterial infections such as tuberculosis (19). In addition, vitamin D prevents excessive reactions of adaptive immune system cells such as activated T-cells, which can lead to autoimmune diseases such as multiple sclerosis or inflammatory bowel disease (21,22). Vitamin D affects the innate immune system through upregulation of the anti-microbial peptide CAMP (23) or the plasma membrane-associated glycoprotein CD14 (24) that functions as a co-receptor for Toll-like receptors. Vitamin D influences the differentiation, growth, and apoptosis of monocytes, dendritic cells, and different T-cells through regulation of the same set of genes and pathways that drive the growth of cancer cells (25). It suggests that the anti-proliferative effect of vitamin D is related to its role in inducing differentiation and apoptosis of cancer cells and its function in controlling immune cells (26). Furthermore, immune cells are an important component of the supportive microenvironment of tumors. Thus, some of the anti-cancer effects of vitamin D may be based on a modulation of the immune component of the microenvironment that is detrimental to tumor survival (27,28). For example, vitamin D can enhance the antibody-dependent cellular cytotoxicity of macrophages and natural killer cells in the context of cancer treatment with monoclonal antibodies. Importantly, the best anti-cancer effect of vitamin D through modulation of the immune system is primarily the prevention of existing tumors, not the prevention of their formation. Every day, thousands of normal cells in each of us turn into cancer cells, but the vast majority of them are detected at an early stage by cytolytic T-cells and eventually eliminated. In this way, activation of cytolytic T-cells by vitamin D is an effective mechanism in preventing the onset of cancer. A seminal epidemiological report published nearly 40 years ago showed that living at lower latitudes, as well as increased sun exposure, reduced the risk of colorectal cancer, both of which led to higher endogenous vitamin D3 production (12). It is also known that 1,25(OH)2D3 can slow the growth of melanoma cells *in vitro* (29). Both observations prompted the idea that low vitamin D status could be a risk factor for cancer. While studies on vitamin D confirm this concept for colorectal cancer, many in vitro studies have concluded that vitamin D will be effective against prostate cancer and breast cancer, as well as lymphoma and leukemia (30).

Although there is a consensus on the cancer-protective effect of vitamin D, there are studies reporting opposing views. Three randomized control studies reported no effect of vitamin D3 supplementation, while their meta-analysis found that it significantly reduced cancer deaths, but there was no reduction in cancer incidence (31-33). Randomized clinical trials of vitamin D supplementation have inconsistent results. There are also opinions that argue that daily vitamin D and calcium supplementation does not have a protective effect against colorectal, breast and all invasive cancers (31,34). However, a Mendelian randomization study based on 74 single-nucleotide polymorphisms associated with 25(OH)D3 serum levels showed that vitamin D status was unlikely to be a causal risk factor for most cancers (35). There are also opinions suggesting that the possible anti-cancer effects of vitamin D3 are not clear in the whole population. Interestingly, the concept of the personalized vitamin D response index in the smaller vitamin D3 study conducted in Finland suggests that 1 in 4 people have a low response to vitamin D, meaning that these individuals should increase their daily dose of vitamin D3 supplementation (36-38). In contrast, those with a high vitamin D response seem to tolerate even a low vitamin D state. Therefore, it is recommended that randomized controlled trials be performed with more parameters, such as body mass index or other markers. In another study, it was reported that a high dosage of 2,000 IU/d of vitamin D together with calcium reduced the incidence of all cancer types in the treatment arm (39,40).

Observational epidemiological studies suggest that low vitamin D status is a risk factor for different types of cancer and that adequate vitamin D3 supplementation is cancer-preventive.

In conclusion, Vitamin D3 is a derivative of cholesterol that acts as a direct regulator of the epigenome and transcriptome of a wide variety of human tissues and cell types, including malignant tumor cells, through its 1,25(OH)2D3 metabolite and its high-affinity receptor VDR. The pronounced effect of vitamin D on proliferation, differentiation and apoptosis of immune cells also has effects on cancer cells. The growth of malignant tumor cells is controlled directly by the same genes and pathways in immune cells or indirectly by modulated immune cells in their microenvironment. Modulation of the immune system also contributes to the anti-cancer effect of vitamin D. It is generally accepted that the protective effect of vitamin D is also applied to neoplastic diseases such as cancer. First of all, the accepted view is that vitamin D does not act on the control of existing tumors, but on the prevention of their formation. Low vitamin D level is a risk factor for different types of cancer. Therefore, adequate vitamin D3 supplementation may prevent cancer in patients with low vitamin D levels, especially in patients with risk factors for cancer development. Vitamin D levels should be closely monitored during and after cancer treatment such as surgery, chemotherapy or radiotherapy, and necessary replacements should be made to keep the levels at optimal levels. Another point is that vitamin D levels are mostly low in this patient group, and even if they are normal, they are usually close to the lower limit of normal. In addition to benefiting from sunlight in these patients, giving vitamin D both with diet and as a supplement may contribute to preventing both cancer formation and recurrence after treatment.

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Original Article

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# Clinical Evaluation of Class II Restorations Made with Bulk-fill Restorative Materials

## Bulk-fill Restoratif Materyallerle Yapılmış Sınıf 2 Restorasyonların Klinik Değerlendirmesi

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## ABSTRACT

**Objective:** The aim of this study was to evaluate the clinical performance of bulk-fill restorative materials applied to Class II cavities retrospectively.

**Methods:** In the study, Class II restorations which were restored with bulk-fill materials in the Department of Restorative Dentistry Selçuk University were determined from the records by using the HIMS (Hospital Information Management System) automation program and the patients were recalled for the controls. Three of the bulk-fill materials used in our clinic [Equia Forte (EF), Tetric EvoCeram Bulk-Fill (TBF) and Filtek Bulk-Fill Posterior Restorative (FBF)] were evaluated. A total of 79 patients and 192 restorations were included in the study. Restorations were assessed according to modified USPHS criteria during the 6$^{th}$, 12$^{th}$ and 24$^{th}$ months from the date of application. The chi-square test was used for statistical analysis of the difference between the groups ($p<0.05$). The Cochran Q test was used for the significance of the difference between the time-dependent changes in each group ($p<0.05$).

**Results:** After 24 months, 139 restorations were evaluated in 64 patients. Thirteen EF and 3 TBF restorations were lost, while no loss was observed in the FBF group. There were clinically acceptable changes in composite restorations. In addition, no statistically significant difference was observed between the clinical performances of these materials in terms of all criteria ($p>0.05$). However, a statistically significant difference was observed between the only EF group and the TBF and FBF groups in terms of retention criteria at 24 months ($p<0.05$).

## ÖZ

**Amaç:** Bu çalışmanın amacı Sınıf 2 kavitelere uygulanan bulk-fill restoratif materyallerin klinik performanslarını retrospektif olarak değerlendirmektir.

**Yöntemler:** Selçuk Üniversitesi, Diş Hekimliği Fakültesi, Restoratif Diş Tedavisi Anabilim Dalı'nda bulk-fill restoratif materyallerle restore edilen Sınıf 2 restorasyonlar HBYS (Hastane Bilgi Yönetim Sistemi) otomasyon programı kullanılarak kayıtlardan tespit edilip hastalar kontrollere çağrıldı. Kliniğimizde kullanılan bulk-fill restoratif materyallerden 3 tanesi olan Equia Forte (EF), Tetric EvoCeram Bulk Fill (TBF) ve Filtek Bulk Fill Posterior Restoratif (FBF) bu çalışmada karşılaştırıldı. Çalışmaya 79 hasta ve 192 adet restorasyon dahil edildi. Restorasyonlar yapılış tarihinden itibaren 6., 12. ve 24. aylarda modifiye USPHS kriterlerine göre değerlendirildi. Gruplar arasındaki farkın istatistiksel analizi için ki-kare testi ($p<0,05$) kullanıldı. Her grubun kendi içinde zamana bağlı değişimi arasındaki farkın anlamlılığı için Cochran Q testi ($p<0,05$) kullanıldı.

**Bulgular:** Yirmi dört ay sonunda 64 hastada 139 restorasyon değerlendirildi, EF grubunda 13 adet, TBF grubunda 3 adet restorasyon klinik olarak başarısız bulunurken; FBF grubunda klinik olarak başarısız restorasyon belirlenmedi. Kompozit restorasyonlarda klinik olarak kabul edilebilir değişiklikler gözlendi. Ayrıca kompozit materyaller arasında klinik performanslarının değerlendirildiği hiçbir kriterde istatistiksel olarak anlamlı fark bulunmadı ($p>0,05$). Yalnızca EF grubu ile TBF ve FBF grupları

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**ABSTRACT**

**Conclusion:** In this study, during a two-year follow-up period, the two bulk fill composite materials showed similar clinical performance; while the high viscosity glass ionomer material showed lower clinical performance.

**Keywords:** Bulk-fill restorative material, high viscosity glass ionomer cement, modified USPHS criteria

**ÖZ**

arasında 24. ayda retansiyon kriteri açısından istatistiksel olarak anlamlı farklılık gözlendi (p<0,05).

**Sonuç:** Bu çalışmada iki yıllık bir takip süresi boyunca, iki bulk fill kompozit materyal benzer klinik performans gösterirken; yüksek viskoziteli cam iyonomer materyal daha düşük klinik performans sergiledi.

**Anahtar Sözcükler:** Bulk-fill restoratif materyal, yüksek viskoziteli cam iyonomer siman, modifiye USPHS kriterleri

## Introduction

Direct and indirect restorations are widely used for restoring posterior teeth in modern dentistry (1-4). Direct restorations are frequently preferred in the posterior region due to their low cost, preservation of healthy tooth tissue, shorter application time, and acceptable clinical performance (3). The use of materials that imitate tooth color is increasing with the development of adhesive systems along with increasing aesthetic concerns. However, an evaluation of long-term clinical follow-up is needed to determine the ideal materials to be used.

With the advancing technology, the aesthetic, mechanical and physical properties of composite resins are being improved. In addition, they are widely used in the posterior region, as they allow the cavity principle, which prevents excess material loss, by minimally invasive dentistry. However, polymerization shrinkage of these materials is still a problem to be solved (5,6). This shrinkage stress can cause negative results in the clinical success parameters of restorations (7,8). It has been tried to reduce the shrinkage stress with approaches such as increasing the amount of filler particles of composite resins or adding monomers with low shrinkage stress, applying different polymerization methods and placement techniques (7).

By applying the restorations in layers of 2 mm with the conventional technique, the polymerization depth is controlled and the polymerization shrinkage stress to occur is expected to decrease. However, in this technique, there is an air gap between the layers and risk of contamination. In addition, the difficulty of adaptation in narrow cavities and the long time to apply this technique can be a disadvantage for clinicians (8-11). It is expected to overcome these problems with the developed bulk-fill composite materials. Bulk-fill composites, which can be applied in layers of 4 mm, save both the patient's and the clinician's time. With the developments in resin-filling technology, the depth of polymerization has been improved by increasing the translucency of bulk-fill composites (12-15). In addition, polymerization shrinkage has been tried to be reduced by adding components such as stress-reducing monomers, higher molecular weight resins, and different polymerization modulators to these materials (16).

Conventional glass ionomer (CGIC) cements are used in the restoration of carious lesions in the posterior region where aesthetic expectations are not high. Advantages such as being chemically bonded to dental tissues, releasing fluoride, being biocompatible, and showing anti-cariogenic properties on the restoration edges increase their preference (17,18). Inadequate color stability, low wear and fracture resistance with low wear limit their use. They are not preferred especially in areas where chewing forces are intense (19).

High viscosity glass ionomer cement (HVGIC) has been produced by eliminating the negative properties of CGIC cement such as moisture sensitivity, low wear/fracture resistance, and insufficient color stability. These materials are also preferred in areas where chewing forces are high (19,20). The manufacturer recommends the use of this material with a surface covering resin. By applying the coating agent to the restoration surfaces, the gloss increases, and the loss of translucency that may occur over time decreases. In addition, irregularities and gaps that may occur after finishing and polishing processes are eliminated, resulting in smoother surfaces. Surface-sealing resins improve the mechanical properties of the restoration by reducing early moisture sensitivity and increasing wear/fracture resistance (21).

There are clinical follow-up studies of bulk-fill restorative materials, the use of which has increased recently, but; there are not many clinical studies comparing them with HVGIC. In this study, Class II restorations previously made in our clinic using bulk-fill restorative materials were evaluated at certain intervals using modified USPH criteria.

In this study, a 24 month clinical follow-up of Class II restorations restored with bulk fill restorative materials was performed. Our hypothesis is that Class II restorations made with bulk fill composites and HVGIC will show similar clinical success at the end of 24 months.

## Methods

### Study Design

This retrospective clinical study was approved by the Faculty of Dentistry Ethics Committee, Selçuk University, (approval no: 2017/14). In the study, Class II restorations restored with two bulk-fill composite resins (TBF, Ivoclar Vivadent, Liechtenstein, FBF Posterior Restorative, 3M ESPE, USA) and an HVGIC (Equia Forte Fil, GC, Tokyo, Japan) were evaluated. Restorations that were completed 6 months and made by the second author

(Bahar İnan) were selected. Clinical records were accessed from the HIMS (Hospital Information Management System) automation program.

**Inclusion and Exclusion Criteria**

For this retrospective clinical evaluation, the restorations meeting the following inclusion criteria were recruited: Patients who were; 1) older than 18 years old, 2) had good general health and oral hygiene, 3) had interface restorations of similar size in their premolars and molars and, 4) were able to attend control appointments were included. Inclusion criteria in the evaluated teeth; teeth were determined as 1) in contact with the opposing tooth, 2) exposed to normal occlusal forces on the dentition, 3) restoration width not exceeding ½ of the intercuspal distance and 4) normal responding to vitality tests without periodontal pathology.

1) Patients with poor oral hygiene, 2) those with active periodontal disease, 3) those with severe bruxism, 4) pregnant and lactating women and, 5) endodontically treated teeth were excluded from the study.

Finally; 79 patients (50 females, 29 males) and 192 restorations meeting the criteria between the ages of 18-53 were included in the study (Figure 1). The patients included in the study signed the informed consent form before the clinical evaluation.

**Restorative Procedures**

The contents, types and manufacturers of the restorative materials used in the study are listed in Table 1. All restorations were performed by the second author (Bahar İnan). The rutin restorative procedure for carious lesions that met the inclusion criteria of this study was as follows:

Cavity preparations were made with diamond burs under water cooling (Green band, NO:12C, SWS Dental, Turkey). The caries tissue was removed using tugten carbide burs at a slow-speed (Meisinger, Germany). Class II slot cavity design was used. No bevels were prepared. All the cavity margins were located in the sound enamel. $Ca(OH)_2$ based cavity lining material (Dycal, Dentsply, Konstanz, Germany) was applied where needed as the base material. The sectional matrix was placed in the cavities and fixed with wooden wedges. The isolation of the operative area was carried out with cotton pellets and suction. The application procedures of the materials used in restorations were as follows.

**Equia Forte Fil (EF):** EF capsule was mixed for 10 seconds with an automatic mixer (TAC 200/S, Linea Tac, Italy). Restorative material was placed into the cavity using the applicator. After the manufacturer's recommended setting time (2.5 minutes), the occlusion was checked and adjusted. Fine-grained diamond burs (Diatech, Colte`ne/Whaledent AG, Altsta¨tten, Switzerland) and Sof-Lex XT discs (3M ESPE, USA) were used for finishing and polishing. Then Equia Forte Coat was applied to the gently dried restoration surfaces and cured for 20 sec.

**Bulk-Fill Composite Resins [Tetric Evo Ceram Bulk Fill (TBF)-Filtek Bulk Fill Posterior Restorative (FBF)]:** The universal bonding agent (Adhese Universal, Ivoclar Vivadent, Liechtenstein) applied to air-dried tooth surface with rubbing action for 20 sec and then medium air pressure was applied to surface for 5 sec. Then restorations were photo-polymerized (Valo, 1,000 mW/cm$^2$, Ultradent, South Jordan, UT, USA) for 10 sec. Then a bulk-fill composite resin (TBF or FBF) was placed in bulk in about 4-mm thickness and then cured with the same curing unit for 20 sec. After the matrix and wedges

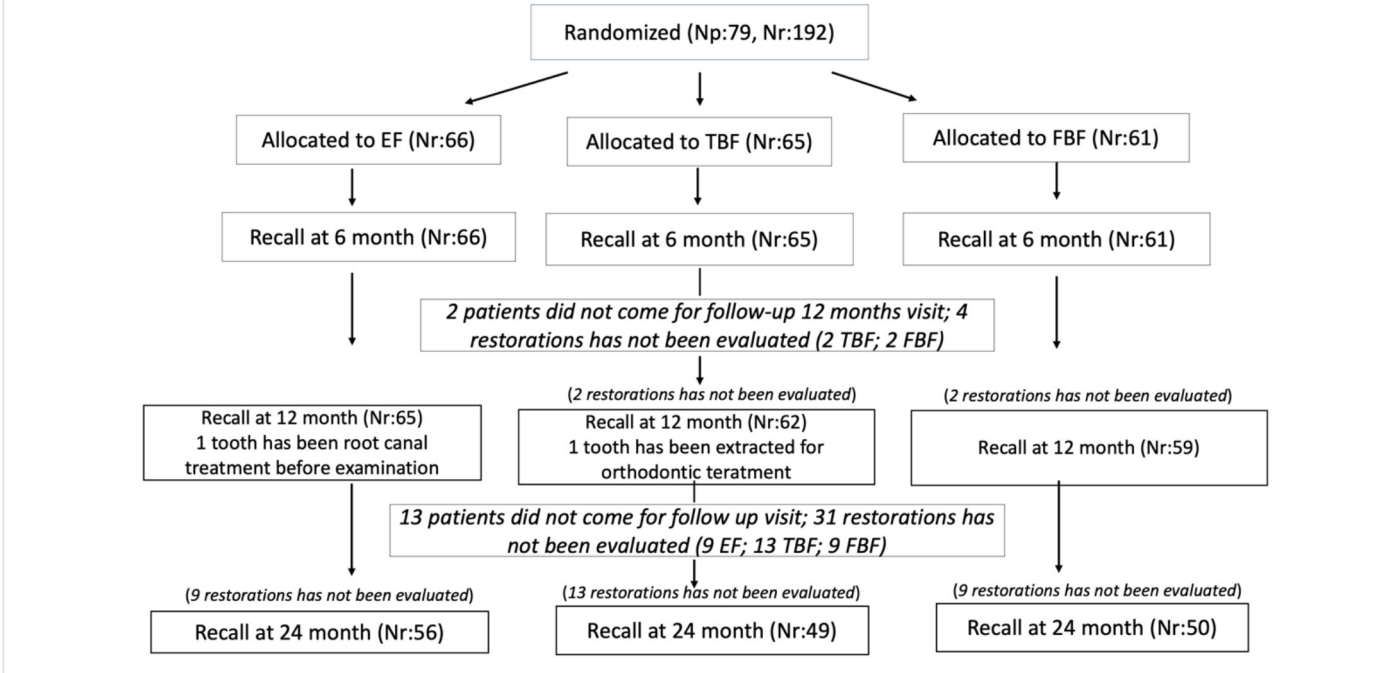


**Figure 1.** Flowchart of the trial

*EF: Equia Forte, TBF: Tetric EvoCeram Bulk-Fill, FBF: Filtek Bulk-Fill*

were removed, the restorations were re-cured for 10 sec from the buccal and palatal/lingual edges. The occlusion was checked and adjusted. Fine-grained diamond burs (Diatech, Colte`ne/Whaledent AG, Altsta¨tten, Switzerland), Sof-Lex XT discs (3M ESPE, USA) and rubber cups and points (Kerr, USA) were used for finishing and polishing.

### Clinical Evaluation of the Restorations

The restorations were evaluated between January 2018 and February 2020 by two experienced investigators according to the modified USPHS criteria (Table 2) including several items on aesthetic, functional, and biological properties. The evaluation was done blinded. The patients were recalled , 12 and 24 months after the restoration placement. The restorations were evaluated in the dental unit under reflector light with mirror and probe. The radiographs taken for the diagnosis of caries or other reasons were evaluated in one- and two-year follow ups. Intraobserver reliability was assessed using Cohen's Kappa, and kappa values of 0.77 and 0.79 were found.

The cumulative retention rates of restorations over the years were calculated using the following equation (ADA Guidelines, 2001) (9,10): Cumulative failure = [(PF + NF)/(PF + RR)] x100. PF: previously lost restorations; NF: number of newly lost restorations seen during the session in which the patient was recalled and evaluated; RR: number of all restorations evaluated during the evaluated session.

### Statistical Analysis

Statistical analysis was performed in SPSS statistical package program 22.0 (IBM Corporation, Armonk, NY, USA). The chi-square test ($p<0.05$) was used for statistical analysis of the difference between groups. The changes within each group

**Table 1.** Materials used in the study

| Product name | Manufacturer | Composition |
|---|---|---|
| Adhese Universal | Ivoclar vivadent/ Liechtenstein | MDP, HEMA Bis-GMA, MCAP, D3MA, ethanol, water, silicon dioxit, camphorquinone, phosphoric acid components |
| Equia Forte Fil | GC/Tokyo, Japan | Powder: 95% strontium fluoro alumino-silicate glass, 5% polyacrylic acid liquid: 40% aqueous polyacrylic acid |
| Equia Forte Coat | GC/Tokyo, Japan | 40-50% methyl methacrylate, 10-15% colloidal silica, 0.09% camphorquinone, 30-40% urethane methacrylate, 1-5% phosphoric ester monomer |
| Tetric EvoCeram Bulk Fill | Ivoclar Vivadent/Lichtenstein | Bis-GMA, UDMA, bis-EMA, barium alumina silicate glass filler, ytterbium fluoride, spherical mixed oxide |
| Filtek Bulk Fill Posterior Restorative | 3M ESPE, St. Paul, MN, USA | Aromatic dimethacrylate (AUDMA), urethane dimethacrylate (UDMA), and 1,12-dodecane dimethacrylate (DDMA), zirconia/silica and ytterbium trifluoride filler |

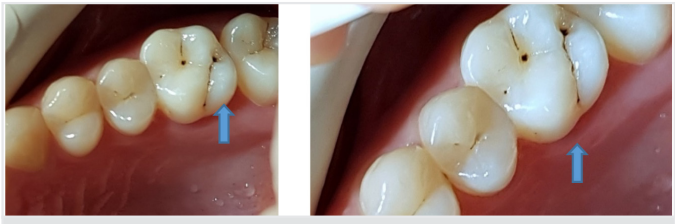

**Figure 2, 3.** Tetric EvoCeram Bulk Fill group with an ***Alpha*** score from all criteria, at 6- month and 12-month follow-ups (tooth number: 15)

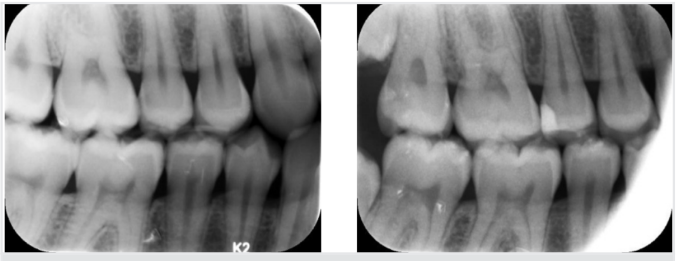

**Figure 4, 5.** Initial and 12-month bite-wing radiographs of the same restoration

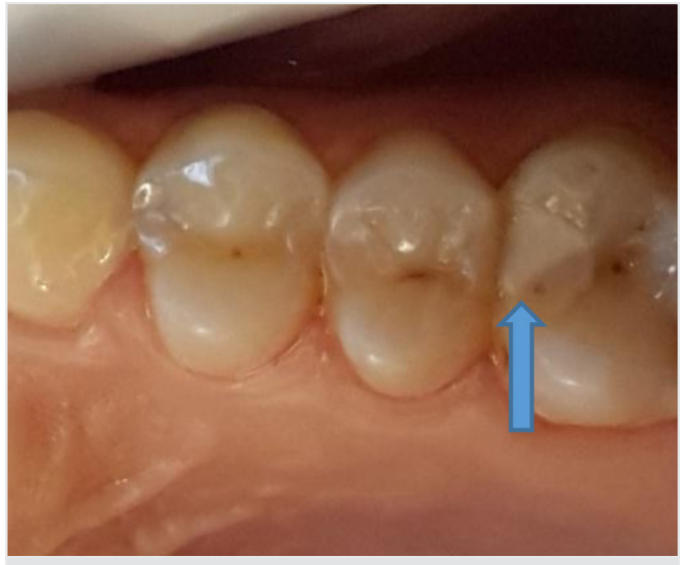

**Figure 6.** Restoration scored with ***Bravo*** for retention in the EF group at 12-month follow-up (tooth number: 16)

*EF: Equia Forte*

between different periods were analyzed by the Cochran Q test ($p<0.05$).

## Results

A total of 192 restorations were evaluated in 79 patients in our study. Of the restorations, 105 (54.6%) were premolars and 87 (45.4%) were molars. (Table 3). Reassessment were performed at 6, 12 and 24 months. At the 6-month follow-up, all patients came to the control appointment. At the 12-month follow-up, 2 patients did not come and 4 restorations (2 TBF, 2 FBF) could not be evaluated. Additionally, before examination, it was observed that 1 tooth was extracted for orthodontic purposes and root canal treatment was applied to 1 tooth. These restorations were excluded from evaluation. One hundred-eighty-six restorations were evaluated in 77 patients. In the 24 month follow-up, 13 more patients did not come and 31 restorations (9 EF, 13 TBF and

**Table 2.** Modified US Public Health Service Criteria

| Modified US Public Health Service Criteria Used in This Study | | |
|---|---|---|
| Retantion | Alpha(A) | No loss of restorative material |
| | Bravo(B) | Partial loss of restorative material |
| | Charlie(C) | Complete loss of restorative material |
| Color match | Alpha(A) | The restoration matches the adjacent tooth structure in color and translucency |
| | Bravo(B) | The mismatch in color and translucency is within the acceptable range |
| | Charlie(C) | The mismatch in color and translucency is outside the acceptable range |
| Marginal discoloration | Alpha(A) | There is no discoloration anywhere on the margin between the restoration and the tooth structure |
| | Bravo(B) | Discoloration is present but has not penetrated along the margin in a pulpal direction |
| | Charlie(C) | Discoloration has penetrated along the margin in a pulpal direction |
| Marginal adaptation | Alpha(A) | There is no visible evidence of a crevice along the margin into which the explorer will penetrate |
| | Bravo(B) | There is visible evidence of a crevice along margin into which the explorer will penetrate or catch |
| | Charlie(C) | The explorer penetrates the crevice, and dentin or base is exposed |
| Secondary caries | Alpha(A) | No evidence of secondary caries |
| | Charlie(C) | Evidence of secondary caries |
| Surface texture | Alpha(A) | The surface of the restoration does not have any defects |
| | Bravo(B) | The surface of the restoration has minimal defects |
| | Charlie(C) | The surface of the restoration has severe defects |
| Anatomic form | Alpha(A) | The restoration is continuous with the existing anatomic form |
| | Bravo(B) | The continuity of restoration with the existing anatomic form teeth partially degraded but clinically acceptable |
| | Charlie(C) | The continuity of restoration with teeth completely deteriorated, need to be replaced |
| Postoperative sensitivity | Alpha(A) | No postoperative sensitivity, after the restorative procedure and during the study |
| | Bravo(B) | Slight sensitivity at any stage of the study |
| | Charlie(C) | Severe sensitivity at any stage of the study |

**Table 3.** Distribution of tested materials according to tooth and arch

| Experimental groups | Maxillar | | Mandibular | | Total |
|---|---|---|---|---|---|
| | Premolar | Molar | Premolar | Molar | |
| Equia Forte Fil | 22 | 15 | 13 | 16 | 66 |
| Tetric EvoCeram Bulk Fill | 26 | 15 | 11 | 13 | 65 |
| Filtek Bulk Fill Posterior Restorative | 22 | 15 | 11 | 13 | 61 |
| Total | 70 | 45 | 35 | 42 | 192 |

9 FBF) could not be evaluated. During the evaluation, retention loss was observed for 13 EF and 3 TBF restorations, root canal treatment was performed on 2 teeth, 1 tooth was extracted, and 10 EF and 3 TBF restorations were renewed. One hundred-fifty-five restorations were evaluated in 64 patients. At the end of 24 months, the rate of patients coming to control was 81%.

The retention rate was 100% for EF, TBF and FBF restorations at six months. At 12-month control, 1 tooth in the EF group was scored with bravo while in the TBT and FBF groups, the retention rate was 100% (Figures 2-6). At the end of 24 months; 13 EF and 3 TBF restorations were lost.

In the EF group, all of the restorative material was lost in 5 restorations. Contact problems occurred due to material loss at the interface of 6 restorations. These restorations were renewed with Estelite Posterior (Tokuyama, Japan) composite resin. Root canal treatment was applied to 2 restorations.

In TBF group, two restorations had partial material loss in proximal area. These restorations were renewed. Root canal treatment was applied to 1 restoration.

No retention loss was observed in the FBF group. The clinical evaluation data of the restorations according to the USPHS criteria are shown in Table 4.

After 24 months, the cumulative retention loss of the EF group was 25%, whereas the cumulative retention loss of the TBF group was 6%. According to the retention data, the difference between the 6$^{th}$, 12$^{th}$, and 24$^{th}$ months evaluations in the EF group was statistically significant ($p<0.05$). At the end of 24 months, the retention data of the EF group were found to be significantly lower than the 6$^{th}$ and 12$^{th}$ months evaluations. Comparing restorative materials while the retention values of the EF group were found to be significantly more unsuccessful than the retention values of the TBF and FBF groups ($p<0.05$); there was no significant difference between TBF and FBF groups ($p>0.05$).

There was no statistically significant difference between the three groups for color match, marginal adaptation, marginal discoloration, secondary caries, anatomical form, surface texture, and postoperative sensitivity criteria ($p>0.05$).

## Discussion

The use of bulk-fill restorative materials in posterior restorations is becoming widespread today. The ease of application of HVGIC and bulk-fill composite materials has increased their preference. In addition, some problems such as the formation of gaps between the layers, the risk of contamination and the difficulties in placing the layers in small spaces can be avoided with this placement method (22).

*In vitro* studies are carried out to examine the properties of the materials available to physicians firstly. However, since the results of these studies do not always reflect the truth, clinical studies are planned and the clinical performances of the materials are evaluated. In our research, Class II restorations made with three bulk-fill materials were followed periodically for 24 months. As a result of the study, it was observed that bulk-fill composite resin materials (TBF and FBF) showed more successful clinical results than high-viscosity glass ionomer cement (EF), and the null hypothesis of the study was rejected.

The retention parameter is very important in evaluating the clinical success of restorative materials. In the study presented by the ADA (23), it was reported that restorations should have a retention rate of at least 90% at the end of 18 months to be considered successful. In this study, the retention rate after 24 months was 76.7% in the EF, 93.8% in the FBF, and 100% in the TBF groups. Considering these data, it could be concluded that EF high viscosity-glass ionomer material applied as bulk fill material was not suitable for routine use in Class II restorations.

Although the use of high-viscosity glass ionomer cement has increased in clinical practice, clinical studies comparing these materials with different restorative materials are very few. There are clinical studies in the literature comparing bulk-fill composites with conventional composites (24-26). Balkaya and Arslan (22) followed Class II restorations made with EF, FBF, and Charisma Smart Composite conventional composite materials for 24 months. As a result of the study, it was observed that the retention values of the EF group (54.3%) were significantly lower, similar to our study. In addition, HVGIC restorative material showed significantly more unsuccessful results than composite materials in terms of the criteria of anatomical form, contact point, marginal adaptation, and surface properties. In another study performed in Class II cavities in primary molars, it was observed that HVGIC was significantly more unsuccessful in terms of retention criteria than a nanohybrid and two bulk-fill composites (27).

Gurgan et al. (28) examined HVGIC and micro-hybrid composite (Gradia Direct Posterior) in Class I and Class II cavities in a 4-year long-term clinical follow-up study. According to the results of the study, there was no significant difference between HVGIC and micro-hybrid composite in terms of

retention, anatomical form, secondary caries, surface structure, postoperative sensitivity and color match; differences were found in marginal adaptation and marginal discoloration (28). In the 6-year results of the same study, the clinical success of restorative materials was found to be similar (29). According to the results of the 2-year follow-up study of Friedl et al. (19); it was reported that the Equia system gave more clinically acceptable results in Class I and Class II cavities with less substance loss. Frankenberger et al. (30) reported that Equia was more successful in Class I restorations than Class II restorations. In these researches, Class I and Class II restorations were evaluated together. In addition, the last study reported that Equia was clinically better than Class II in Class I restorations. This might explain why HVGIC and composite materials showed similar retention values in these studies.

In another long-term clinical study, the clinical performances of two different high-viscosity glass ionomers (Equia Fil and Riva SC) applied to Class I and II cavities were evaluated using USPHS criteria (31). Class II restorations in the Equia Fil group were found to be more successful in terms of retention, marginal adaptation, and anatomical form parameters than in the Riva SC group. Restorations requiring repair were not evaluated as unsuccessful in this study. In our research, restorations requiring repair were deemed unsuccessful. This condition can explain inconsistent results.

In the literature, material losses in Class II restorations made with high-viscosity glass ionomers have been reported in the proximal regions (32,33). After the HVGIC is placed, the application of a surface coating agent is necessary for the initial curing phase of the material. The structural strength of the material may be adversely affected if the agent is not applied effectively. The material losses detected at the proximal surface may have been caused by the inadequate application of coating agents to these regions. In addition, these materials are subjected to wear due to chewing forces and environmental factors. Metal matrix bands are used in the made of proximal surface restorations in our clinic. Glass ionomers can form chemical bonds with metal matrix bands as they are placed in cavities, and the force generated during removal of the matrix bands can create microcracks in glass ionomers (33). In our study, proximal to occlusal or total losses were observed in restorations with a "Charlie" score in terms of retention. It can be thought that material losses could occur due to wear of the surface coating agent and deterioration of the structural strength of the glass ionomer cement.

**Table 4.** 6th, 12th and 24th months clinical evaluation of restorations according to US Public Health Service Criteria

| | | Equia Forte | | | Tetric EvoCeram Bulk Fill | | | Filtek Bulk Fill Posterior Restorative | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 6 months | One-year | Two-year | 6 months | One-year | Two-year | 6 months | One-year | Two-year |
| Retantion | A | 66/66 (100%) | 64/65 (98.5%) | 56/43 (76.7%) | 65/65 (100%) | 62/62 (100%) | 46/49 (93.8%) | 61/61 (100%) | 59/59 (100%) | 50/50 (100%) |
| | B | - | 1/65 (1.5%) | - | - | - | - | - | - | - |
| | C | - | - | 56/13 (23.2%) | - | - | 3/49 (7.2%) | - | - | - |
| Color match | A | 66/66 (100%) | 65/65 (100%) | 37/43 (86.04%) | 65/65 (100%) | 62/62 (100%) | 42/46 (91.3%) | 61/61 (100%) | 59/59 (100%) | 45/50 (90%) |
| | B | - | - | 6/43 (13.9%) | - | - | 4/46 (8.7%) | - | - | 5/50 (10%) |
| | C | - | - | - | - | - | - | - | - | - |
| Marjinal adaptation | A | 66/66 (100%) | 63/65 (96.9%) | 40/43 (93.02%) | 63/65 (96.9%) | 60/62 (97.8%) | 42/46 (91.3%) | 61/61 (100%) | 59/59 (100%) | 46/50 (92%) |
| | B | - | 1/65 (1.5%) | 2/43 (4.6%) | 2/65 (3.07%) | 2/62 (3.2%) | 2/46 (8.7%) | - | - | 4/50 (8%) |
| | C | - | 1/65 (1.5%) | 1/43 (2.3%) | - | - | - | - | - | - |
| Marjinal discoloration | A | 66/66 (100%) | 65/65 (100%) | 38/43 (88.3%) | 65/65 (100%) | 62/62 (100%) | 42/46 (91.3%) | 60/61 (98.4%) | 58/59 (98.3%) | 46/50 (92%) |
| | B | - | - | 5/43 (11.6%) | - | - | 3/46 (6.5%) | 1/61 (1.6%) | 1/59 (1.7%) | 4/50 (8%) |
| | C | - | - | - | - | - | 1/46 (2.1%) | - | - | - |

**Table 4.** Continued

| | | Equia Forte | | | Tetric EvoCeram Bulk Fill | | | Filtek Bulk Fill Posterior Restorative | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 6 months | One-year | Two-year | 6 months | One-year | Two-year | 6 months | One-year | Two-year |
| **Secondary caries** | A | 66/66 (100%) | 65/65 (100%) | 41/43 (95.3%) | 65/65 (100%) | 62/62 (100%) | 46/46 (100%) | 61/61 (100%) | 59/59 (100%) | 49/50 (98%) |
| | C | - | - | 2/43 (4.6%) | - | - | - | - | - | 1/50 (2%) |
| **Surface texture** | A | 65/66 (98.5%) | 64/65 (98.5%) | 40/43 (93.02%) | 65/65 (100%) | 61/62 (98.4%) | 44/46 (95.6%) | 61/61 (100%) | 59/59 (100%) | 49/50 (98%) |
| | B | 1/66 (1.5%) | 1/65 (1.5%) | 3/43 (6.9%) | - | 1/62 (1.6%) | 2/46 (4.4%) | - | - | 1/50 (2%) |
| | C | - | - | - | - | - | - | - | - | - |
| **Anatomic form** | A | 66/66 (100%) | 63/65 (96.9%) | 41/43 (95.3%) | 65/65 (100%) | 62/62 (100%) | 46/46 (100%) | 61/61 (100%) | 59/59 (100%) | 49/50 (98%) |
| | B | - | 1/65 (1.5%) | 1/43 (2.3%) | - | - | - | - | - | 1/50 (2%) |
| | C | - | 1/65 (1.5%) | 1/43 (2.3%) | - | - | - | - | - | - |
| **Postoperative sensitivity** | A | 64/66 (96.9%) | 64/65 (98.5%) | 41/43 (95.3%) | 65/65 (100%) | 62/62 (100%) | 45/46 (97.8%) | 60/61 (98.4%) | 59/59 (100%) | 50/50 (100%) |
| | B | 1/66 (1.5%) | 1/65 (1.5%) | 1/43 (2.3%) | - | - | 1/46 (2.2%) | 1/61 (1.6%) | - | - |
| | C | 1/66 (1.5%) | - | 1/43 (2.3%) | - | - | - | - | - | - |

A: Alpha, B: Bravo, C: Charlie

Although HVGIC's translucency is higher than conventional glass ionomers, color matching is still improving. According to the results of the study, the color match and marginal discoloration values of all materials were found to be similar. Even if the oral hygiene status was considered in the inclusion criteria of the patients, the differences in the amount of consumption of coloring foods and drinks might be effective in finding similar results. In addition, as the maturation time of glass ionomers increases, the translucency ratio also increases (34). There are also studies showing that color match improves over time (35).

The surface structure and anatomical form of restorations may be relevant to specific characteristics such as the patient's habits, diet, or the type and content of materials. All the materials we used in our study showed clinically successful results at the end of 24 months in terms of surface structure and anatomical form parameters. Composite resins have been found successful in many long-term clinical follow-up studies. The similar results of the glass ionomer restorations in our study may indicate that their mechanical properties have been improved compared to conventional glass ionomers.

There was no significant difference between the restorative materials at the end of 24 months in terms of postoperative sensitivity and secondary caries data. The fact that the patients had good oral hygiene habits, and the fluoride release feature of EF might be effective in the absence of secondary caries. Postoperative sensitivity is closely related to the depth of the cavity and traumatic cavity preparation (36). In the restoration procedure, calcium hydroxide based cavity lining material was placed close to the pulp in very deep cavities. The restorations in the study were made with adhesive system applied in self-etch mode. No acid application might have a significant effect on the absence of postoperative sensitivity.

**Study Limitations**

This research study was conducted retrospectively. Although specific criteria were observed when including patients in the study, it was not possible to standardize as much as prospective studies. In addition, since the 24-month follow-up coincided with the COVID-19 pandemic, the rate of patients coming to control appointments decreased.

## Conclusion

At the end of 24 months, bulk fill composite materials showed successful results in all clinical parameters. HVGIC material was clinically unsuccessful only in terms of the retention criteria. These results indicate that the use of HVGICs in Class II restorations should be limited.

### Ethics

**Ethics Committee Approval:** This retrospective clinical study was approved by the Faculty of Dentistry Ethics Committee, Selçuk University, (approval no: 2017/14).

**Informed Consent:** Obtained.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.G., B.İ., N.Ç., Concept: M.G., B.İ., N.Ç., Design: M.G., B.İ., N.Ç., Data Collection or Processing: M.G., B.İ., N.Ç., Analysis or Interpretation: M.G., B.İ., N.Ç., Literature Search: M.G., B.İ., N.Ç., Writing: M.G., B.İ., N.Ç.

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Original Article

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# Microhardness, Degree of Conversion, and Water Sorption/ Solubility of Non-expired and Expired (Two and Three Years) Dental Composites

## Son Kullanma Tarihi Geçmiş (İki ve Üç Yıl) ve Geçmemiş Dental Kompozitlerin Mikrosertliği, Dönüşüm Oranı ve Su Emilimi/Çözünürlüğü

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## ABSTRACT

**Objective:** The aim of this study was to compare the microhardness, degree of conversion, and water sorption/solubility of two- and three-year expired dental composites (Filtek Ultimate Universal) with the non-expired equivalent.

**Methods:** The prepared specimens (diameter =8 mm; thickness =2 mm) were subjected to Vickers hardness testing on the top and the bottom surfaces, and the degree of conversion was calculated based on the bottom/top hardness ratio. Further, water sorption and solubility were measured after immersion in distilled water for 1, 7, and 28 d. For statistical analysis, Shapiro-Wilk test, one-way analysis of variance, Kruskal-Wallis test, repeated analysis of variance and Friedman test were used ($p<0.05$).

**Results:** No significant changes in microhardness, degree of conversion, or water solubility were observed between any of the groups. However, the water sorption of the non-expired dental composite was higher than that of the three-year expired group after 28 d. Further, the water sorption/solubility of all of the expired and non-expired materials changed over time between 1 and 28 d.

**Conclusion:** Thus, the non-expired, two-year expired, and three-year expired dental composites exhibited similar microhardness, conversion degree, and water solubility characteristics. However, the degradation of dental composites is a complex process, and dentists are advised to adhere to expiration dates.

**Keywords:** Aging, composite resin, dental restoration, dentistry, hardness

## ÖZ

**Amaç:** Bu çalışmanın amacı, iki ve üç yıllık son kullanma tarihi geçmiş dental kompozitlerin (Filtek Ultimate Universal) tarihi geçmemiş kompozitlere göre mikrosertliği, dönüşüm oranı ve su emilimi/çözünürlüğünü karşılaştırmaktır.

**Yöntemler:** Hazırlanan örneklerin (çap =8 mm; kalınlık =2 mm) alt ve üst yüzeylerine Vickers sertlik testi uygulandı ve alt/üst sertlik oranına göre dönüşüm oranı hesaplandı. Ayrıca, 1, 7 ve 28 gün distile su içinde bekletildikten sonra su emilimi ve çözünürlüğü ölçüldü. İstatistiksel analiz için Shapiro-Wilk testi, tek yönlü varyans analizi, Kruskal-Wallis, tekrarlayan varyans analizi ve Friedman testi kullanıldı ($p<0,05$).

**Bulgular:** Mikrosertlik, dönüşüm oranı veya suda çözünürlük açısından gruplar arasında anlamlı fark bulunamadı. Fakat, son kullanma tarihi geçmemiş dental kompozitlerin üç yıllık dental kompozitlere göre 28. gündeki suda emilimi daha yüksekti. Ayrıca, tüm son kullanma tarihi geçmiş ve geçmemiş materyallerin su emilimi/çözünürlükleri 1 ve 28. gün arasında zamanla değişti.

**Sonuç:** Son kullanma tarihi iki ve üç yıl geçmiş ve geçmemiş dental kompozitler mikrosertlik, dönüşüm oranı ve suda çözünürlük açısından benzer karakteristikler sergiledi. Fakat, dental kompozitlerin degredasyonu karmaşık bir süreçtir ve diş hekimlerine son kullanma tarihlerine uymaları tavsiye edilir.

**Anahtar Sözcükler:** Yıllanma, kompozit rezin, dental restorasyon, diş hekimliği, sertlik

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## Introduction

Dental composites are common materials in dentistry, where the clinical behavior and properties thereof are determined by the material structure, degradation rate, and age (1,2). Once a composite material is applied in a dental cavity, it is difficult to prevent degradation (3,4). This degradation is a complex process and can be classified as either intraoral degradation due to mechanical, chemical and physical effects, or extraoral degradation due to storage conditions and aging (2).

An expiration date is based on the time period that a dental composite can maintain its stability, and is determined by the manufacturer (5). A small amount of dental composite is often used in dental practice, after which the remaining material may be stored until its expiration date (6). However, the use of expired dental composites can lead to fracturing, wear, and discoloration (2). Despite these issues, some dentists continue to use expired dental composites to avoid wasting excess materials (6). Thus, it is important to evaluate the characteristics of expired dental composites and predict their clinical performance.

Hardness, strength, modulus, and water sorption are important composite properties that are directly related to the degree of monomer to polymer conversion within the composite (7). Specifically, insufficient conversion can compromise the mechanical properties of the material, especially hardness (8,9). As the degree of conversion decreases, the free space in the polymeric network increases, which facilitates water diffusion across the network (9).

This study aimed to broadly evaluate and compare the microhardness, conversion degree, water sorption, and solubility of two- and three-year expired dental composites with the non-expired equivalent. The null hypothesis was that expiration date had no effect on the microhardness, degree of conversion, and water sorption-solubility of dental composites.

## Methods

### Preparation of Specimens

Non-expired, two-year expired, and three-year expired universal dental composites (Filtek Ultimate Universal, 3M ESPE, Saint Paul, USA) were compared. All of the dental composites were kept in the refrigerator before the study. The details of the composite are given (Table 1). Nine cylindrical specimens (diameter =8 mm; thickness =2 mm) for each experimental group (non-expired, two-year expired, and three-year expired) were prepared in a Teflon mold with a glass slide covering the surface of the polyester matrix. A single layer of the composite material was transferred into the mold and light cured using a polymerization unit (Elipar Free Light 2, 3M ESPE, Saint Paul, USA) according to the manufacturer's instructions. The top surface of each specimen was marked using a waterproof pen. The specimens were removed from the mold and stored in distilled water at 37 °C for 24 h to facilitate maximum polymerization before testing.

### Vickers Microhardness and Degree of Conversion

Vickers microhardness testing was conducted using a microhardness tester (Struers Duramin 5, Struers A/S, Ballerup, Denmark). Five indentations were conducted at different locations on the top and bottom surfaces of each specimen under a load of 1.96 N for 10 s. The mean value of the five indentations were used to determine the hardness of the top and bottom surfaces. The degree of conversion was evaluated based on the ratio of bottom hardness to top hardness.

### Water Sorption and Solubility

Water sorption and solubility were evaluated using the same specimens after microhardness testing. The procedures given in the ISO 4049:2000 standard were used. However, the specimen dimensions did differ from the standard procedure. The constant mass of the specimens was determined by placing the specimens in a desiccator containing calcium sulfate ($CaSO_4.2H_2O$) (Edukim, Turkey) at 37±1 °C for 24 h, followed by weighing using an electronic analytical balance (Kern &Sohn GmnH, ABJ 220-4M, Germany) with 0.0001 g accuracy. The procedure was repeated until each specimen reached constant mass (M1; μg), where the mass did not fluctuate by more than ±0.1 mg over 24 h (10). Thereafter, the dimensions of the specimens were measured using a digital caliper to calculate the volume (V; $mm^3$), where the diameter was taken as the mean of two diameter measurements at right angles, and the thickness was taken as the mean of the thickness at the center and at four equally spaced points on the circumference.

All specimens were placed in 2 mL distilled water in an incubator at 37±1 °C for 1 d. The specimens were removed, carefully dried with absorbent paper, and weighed using the analytical balance (M2a). The specimens were placed back in the desiccator, and the constant mass procedure was repeated until a constant mass was achieved for 24 h (M3a). The specimens were incubated in distilled water for 7 and 28 d, where the distilled water was refreshed every day. The specimens were removed from the water after the respective periods, weighed using the analytical balance to determine M2b and M2c, respectively, and placed

**Table 1.** The composition of the dental composite used in the present study

| Name | Manufacturer | Main components | Type | Application procedure | Shade |
|---|---|---|---|---|---|
| Filtek Ultimate Universal (FUU) | 3M ESPE, St.Paul, MN, USA ® | Bis-EMA, Bis-GMA, UDMA, TEGDMA, PEGDMA, silica, zirconia filler, zirconia/silica cluster filler | Nanofill composite | Curing time is 20 s for 2 mm enamel composite layer | A1 Enamel |

back in the desiccator to achieve constant masses M3b and M3c, respectively. Water sorption ($W_{sp}$) and solubility ($W_{sl}$) (μg/mm$^3$) were determined based on M1 for the initial state, M2a and M3a for 1 d, M2b and M3b for 7 d, and M2c and M3c for 28 d as follows:

$$Wsp = \frac{M2(a,b,c) - M3(a,b,c)}{V}$$

$$Wsl = \frac{M1 - M3(a,b,c)}{V}$$

### Scanning Electron Microscope (SEM) Analysis

One specimen from each group was selected to observe surface morphology. The selected specimens were dried in a dehumidifier with silica gel for 72 hours. They were coated with gold, and observed with a scanning electron microscope [EVO LS 10, Zeiss, Germany)] under x3,500 magnifications for qualitative analysis of the surface.

### Statistical Analysis

Statistical analysis was performed using SPSS 23V software. The compliance to normal distribution was analyzed using the Shapiro-Wilk test. The normally distributed data were analyzed using one-way analysis of variance. The Kruskal-Wallis test was used for the comparison of non-normally distributed data in terms of groups. Repeated analysis of variance was used to compare three or more normally distributed datapoints within the group, while the Friedman test was used to compare non-normally distributed data. The results were presented as mean ± standard deviation and median (minimum-maximum). The significance level was set at p<0.050.

## Results

There was no statistically significant difference between the nonexpired (p=0.162), two-year expired (p=0.827), or three-year expired groups (p=0.225) in terms of bottom and top microhardness values and degrees of conversion (Figure 1, Table 2).

The inter- and intragroup comparisons of water sorption and solubility indicated that there were some statistically significant differences in the water sorption and solubility behavior of the composites (Figure 2, Table 3). Specifically, the median water sorption of the non-expired group was significantly higher (p=0.017) than that of the three-year expired group after 28 d. Further, there was a statistically significant difference in the median water sorption over time in the non-expired (p=0.002), two-year expired (p<0.001), and three-year expired groups (p=0.001), where the median water sorption after 28 d water was significantly higher than after 1 d for each group. In addition, the median value of the three-year expired group was higher after 28 d than the median values after both 1 and 7 d.

The mean water solubility did not differ between the groups at any time point (p>0.050). However, there was a statistically significant difference in the mean water solubility over time in the nonexpired (p<0.001), two-year expired (p<0.001), and three-year expired groups (p<0.001). Specifically, the mean water solubility of the nonexpired and two-year expired groups was significantly higher after 28 d compared to 1 and 7 d, while

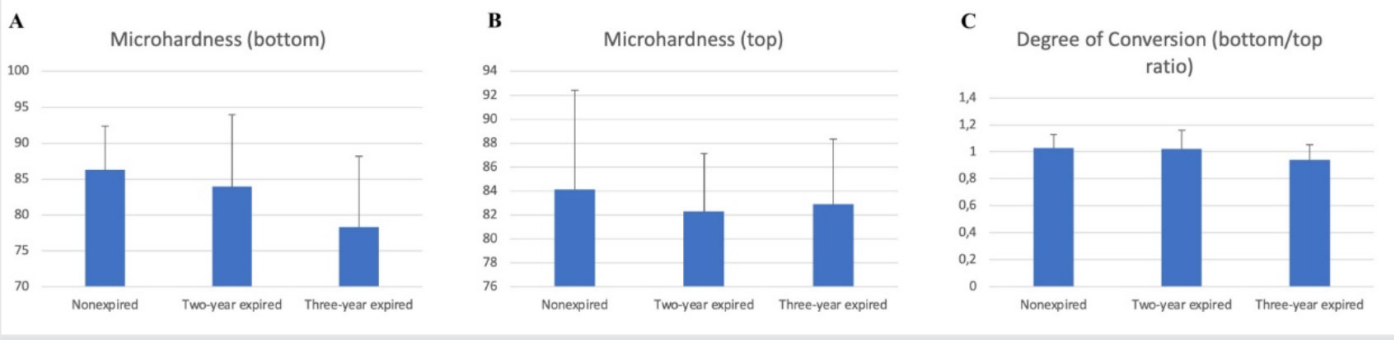


**Figure 1.** Mean and standard deviations graphics for bottom microhardness (A), top microhardness (B) and degree of conversion (C)

**Table 2.** Comparison of three groups in terms of bottom and top microhardness and degree of conversion values

| | | Non-expired | Two-year expired | Three-year expired | p* |
|---|---|---|---|---|---|
| Microhardness (bottom) | Mean ± SD | 86.31±6.07 | 83.94±9.98 | 78.28±9.86 | 0.162 |
| | Median (min.-max.) | 85.46 (78.38-96.68) | 81.12 (74.00-105.94) | 81.48 (61.52-94.80) | |
| Microhardness (top) | Mean ± SD | 84.10±8.32 | 82.27±4.84 | 82.92±5.39 | 0.827 |
| | Median (min.-max.) | 82.68 (73.04-101.98) | 83.36 (76.68-90.10) | 83.78 (73.64-90.02) | |
| Degree of conversion (bottom/top ratio) | Mean ± SD | 1.03±0.10 | 1.02±0.14 | 0.94±0.11 | 0.225 |
| | Median (min.-max.) | 1.00 (0.91-1.23) | 1.00 (0.86- 1.23) | 0.96 (0.73- 1.09) | |

*Analysis of variance, SD: Standard deviation, min: Minimum, max: Maximum

the mean water solubility of the three-year expired group differed significantly between all three time points.

The representative SEM images of each group were shown in Figure 3. Although they had similar appearance at x1,500 magnification, three-year expired dental composite had more irregularities on its surface at x3,500 magnification. Some spaces were observed on all of the three specimens at different magnifications.

## Discussion

Microhardness, degree of conversion, and water sorption/solubility are important properties of dental composites, and serve as important predictors for material performance. The null hypothesis that expiration date had no effect on conversion degree, microhardness and water sorption/solubility of dental composites was partially confirmed by the results (Tables 2, 3), as there was only statistically significant difference in the water sorption of the groups after 28 d.

The resistance of the dental composite to different forces in the mouth was evaluated based on microhardness (11,12). The longevity, strength, and durability of the composite in load bearing areas are also dependent on hardness (13). The hardness of a dental composite is affected by material type, water absorption, aging, and reactions on the material surface (14). Due to its effect on other physical properties, hardness is an important property in characterizing and ranking dental restorative materials (15). A greater hardness can be achieved via extensive polymerization and cross-linking (16), and is affected by various material characteristics such as monomer system, dilution concentration, initiator concentration, and loaded particle type and amount (17). Previous research indicated that the minimum Vickers hardness of a dental composite was 50 (18), where all of the mean hardness Vickers measurements in

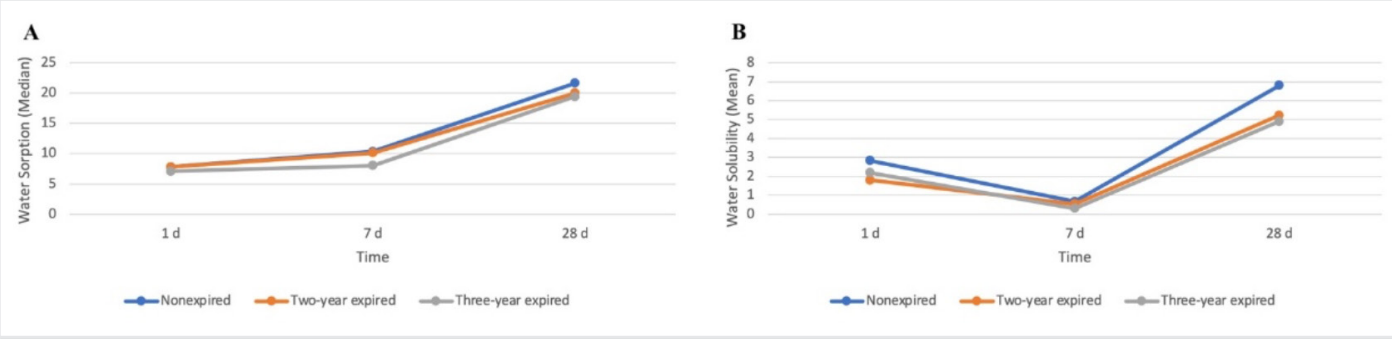


**Figure 2.** Line chart of the values of water sorption **(A)** and water solubility **(B)**

**Table 3.** Comparison of water sorption and solubility in terms of inter and intragroups

| | | Non-expired | Two-year expired | Three-year expired | p |
|---|---|---|---|---|---|
| Water sorption (μg/mm³) after 1 d | Mean ± SD | 7.79±2.25 | 7.46±2.54 | 7.88±1.60 | 0.927[1] |
| | Median (min.-max.) | 7.77 (3.88-12.37)$^{A}$ | 7.77 (4.00-12.50)$^{A}$ | 7.07 (6.00-11.00)$^{A}$ | |
| Water sorption (μg/mm³) after 7 d | Mean ± SD | 11.44±5.55 | 11.30±4.77 | 8.80±2.71 | 0.279[1] |
| | Median (min.-max.) | 10.31 (3.85-24.07)$^{AB}$ | 10.09 (5.56-19.44)$^{AB}$ | 8.00 (5.88-14.81)$^{A}$ | |
| Water sorption (μg/mm³) after 28 d | Mean ± SD | 21.98±1.53 | 19.75±1.76 | 20.01±2.25 | 0.017[1] |
| | Median (min.-max.) | 21.65 (20.19-25.24)$^{aB}$ | 20.00 (16.67-22.00)$^{abB}$ | 19.42 (18.18-25.49)$^{bB}$ | |
| p** | | **0.002[2]** | **<0.001[2]** | **0.001[2]** | |
| Water solubility (μg/mm³) after 1 d | Mean ± SD | 2.83±2.65$^{A}$ | 1.80±0.71$^{A}$ | 2.18±1.06$^{A}$ | 0.442[3] |
| | Median (min.-max.) | 2.83 (-0.97-8.25) | 1.92 (0.95-2.78) | 2.78 (0.00-3.00) | |
| Water solubility (μg/mm³) after 7 d | Mean±sd | 0.66±1.32$^{A}$ | 0.53±1.62$^{A}$ | 0.30±1.53$^{B}$ | 0.876[3] |
| | Median (min.-max.) | 0.93 (-0.97-3.09) | 0.00 (-1.98-3.00) | 0.00 (-2.02-2.78) | |
| Water solubility (μg/mm³) after 28 d | Mean±sd | 6.81±1.43$^{B}$ | 5.23±1.54$^{B}$ | 4.90±1.85$^{C}$ | 0.050[3] |
| | Median (min.-max.) | 6.54 (4.81 - 9.28) | 4.81 (3.67-8.00) | 4.85 (2.91-7.84) | |
| p** | | <0.001[4] | <0.001[4] | <0.001[4] | |

†[1]Kuskal Wallis test, [2]Friedman test, [3]Analysis of variance, [4]Repeated analysis of variance, a-b: No significant difference for same lowercase among groups, A-C: No significant difference for same uppercase among duration

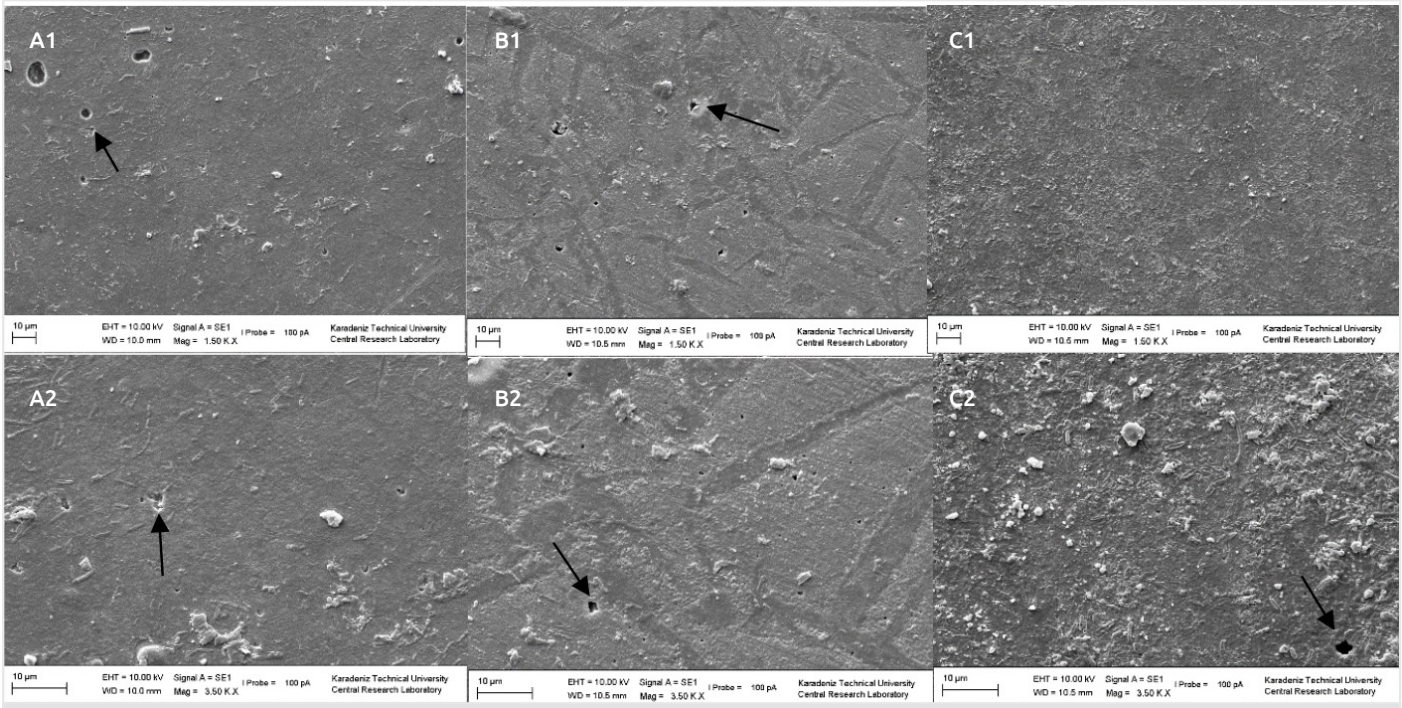


**Figure 3.** Sem images of non-expired (A1-A2), two-year expired (B1-B2) and three-year expired (C1-C2) dental composites at x1,500 and x3,500 magnifications, respectively. The black arrows show the spaces on dental composites at different magnifications

this study were substantially higher than 50. Further, there was no statistically significant difference between the hardness of the two expired groups and the nonexpired group. This was similar to the findings of a previous study, which reported that dental composites used 180 d after their expiration date did not have a significantly different hardness, with the exception one of one dental composite type (TPH Spectrum, Dentsply, USA) (6).

The degree of monomer to polymer conversion in a dental composite has an effect on its mechanical properties, color stability, and biocompatibility. The degree of conversion of a light-cured composite is dependent on the factors that affect light penetration, such as light scattering among particles, light absorbance by the photoinitiators, and pigment effects (19,20). More specifically, the parameters that affect the polymerization of dental composites include composition (e.g., photoinitiators, fillers, and organic matrix) (21), the light curing time and equipment (22), sample thickness (23), post-irradiation (24), and temperature of the material (25). All of these parameters were standardized in this study to isolate the effects of expiration date. The best indirect determinants of degree of conversion are Vickers and Knoop surface hardness measurements (26,27), while Fourier-transform infrared (FTIR) is considered a less sensitive technique (28). Polymerization might continue for 24 h after light curing (16), thus the bottom and top Vickers hardness measurements were only conducted 24 h after of light curing. A bottom/top hardness ratio of >0.8 is often accepted as the threshold value (29,30). All values in this study were above 0.8 due to optimal polymerization in under *in vitro* conditions. Further, it was impossible to conduct multiple hardness measurements at the same location on the composite specimens, which might affect the results. Overall, there was no statistically significant difference in the degree of conversion among the groups. However, the three-year expired dental composite did exhibit the lowest degree of conversion. This may be attributed to the plasticization effect of the residual monomers (9), which can decrease the clinical success of the composite (19).

Water sorption and solubility of the two-year and three-year expired composites were compared with the nonexpired equivalent over immersion periods of 1, 7 and 28 d. All of the groups exhibited a continuous increase in water sorption over the 28 d period, where the water sorption was statistically higher after 28 d compared to 1 d. According to the ISO 4049 standard, the maximum allowed water gain is <40 μg/mm$^3$ after 28 d (10). The water sorption of the nonexpired group was statistically higher than that of the expired groups after 28 d. This may be a desirable phenomenon, as the absorbed water can distend the matrix and minimize the shrinkage effect of polymerization (31). However, a larger coefficient of expansion than shrinkage value is not desirable, as this can lead to further stress on the restoration and tooth. These effects of water sorption should be further investigated based on microleakage or shrinkage studies with expired composites.

The water solubility of all of the samples was less than 7.5 μg/mm$^3$, and there was no statistically significant differences between the groups at any time point. Thus, all three groups exhibited acceptable solubility behavior according to the ISO 4049 standard (10). The water solubility of a dental material can be correlated with its water sorption because water penetration into the material can lead to the leaching of unreacted components (32). However, this was not observed in the present study, where the three groups did not have the same ranking with respect to water sorption and the solubility level.

A previous study (33) on one-year expired dental composites reported similar findings to the present study regarding mechanical properties, including hardness and degree of conversion. A similar study also reported that there was no significant change in the modulus of elasticity and Vickers microhardness in one-year expired dental composites (2), while another study (34) on 15-month expired dental composites reported that the flexural performance did not change significantly. Further, a study (35) on the light curing of resins reported that the light curing properties remained constant for seven years after expiration, regardless of the storage conditions. The presence of preservatives, the temperature fluctuations, ambient conditions such as light, humidity and storage conditions may affect the characteristics of dental materials. As the materials are polymeric, their performances depend on the rate of degradation (36). The dental composites used in the present study were stored in the refrigerator and did not undergo significant changes in terms of microhardness, degree of conversion, or water solubility over time. This may be because of optimal ambient conditions and storage temperature.

The manufactures generally recommend the dental materials to be used up to 6 months after their expiration date. However, dentists use only small amounts of dental composites (6) and these materials may be used more than 6 months after their expiration date for some diagnostic purposes such as mock-up and temporary crowns (37). In this regard in this in vitro study two-year expired and three-year expired dental composites were compared with their non-expired equivalent.

### Study Limitations

While these properties are important, other parameters such as radiopacity, optical properties, and surface roughness should be investigated further in expired dental composites. In addition, laboratory studies do not accurately represent clinical conditions, as they cannot fully reflect intraoral conditions such as saliva, masticatory forces, and the different irradiation distances of composite materials at various cavity depths. Thus, further investigation of other parameters and clinical studies are recommended.

## Conclusion

Within the limitations of this study, it can be concluded that two- and three-year expired dental composites exhibit similar characteristics in terms of microhardness, degree of conversion, and water solubility to the nonexpired equivalent. As the degradation of dental composites is a complex process, it is advised that dentists adhere to expiration dates. Further investigation of more properties of expired composites is recommended to provide a better understanding of the effects of aging beyond the expiration date.

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### Ethics

**Ethics Committee Approval:** There is no need for an ethics committee document.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

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

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

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Original Article

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# The Role of Clinical and Inflammatory Parameters to Predict the Success of Medical Treatment in Patients with Tubo-ovarian Abscess

## Tubo-ovaryan Apseli Hastalarda Medikal Tedavinin Başarısını Öngörmede Klinik ve Enflamatuvar Parametrelerin Rolü

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## ABSTRACT

**Objective:** To examine the role of hematological inflammation markers and clinical findings on the day of hospitalization in predicting medical treatment failure in patients with tubo-ovarian abscess (TOA).

**Methods:** A total of 49 patients with TOA who were hospitalized in our hospital were included in this study. The patients whose clinical findings, biochemical inflammation-related markers or radiological findings that did not improve despite the medical treatment and surgery or minimally-invasive drainage performed were enrolled into the medical treatment failure group (n=12). Demographic data (age, weight, gravidity, parity, abortion, presence of abdominal guarding, rebound, vaginal discharge, cervical motion tenderness, fever, length of stay), laboratory results [C-reactive protein (CRP), procalcitonin, white blood cell count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio] and radiological reports (abscess size) of the patients on the day of hospitalization were obtained from hospital records.

**Results:** Cervical motion tenderness, CRP levels and the length of stay of the medical failure group were higher than successful medical treatment group on the day of hospitalization ($p<0.05$ for all). CRP level had diagnostic adequacy in predicting the success of medical treatment of TOA (AUC =0.71, p=0.03). At the time of admission, CRP level <144 mg/L had 88.2% positive predictive value (PPV).

## ÖZ

**Amaç:** Tubo-ovaryan apseli (TOA) hastalarda medikal tedavi başarısızlığını öngörmede hastaneye yatış günündeki hematolojik enflamasyon belirteçleri ve klinik bulguların rolünü incelemektir.

**Yöntemler:** Bu çalışmaya hastanemizde yatan toplam 49 TOA'lı hasta dahil edildi. Medikal tedavi ve cerrahi veya minimal invaziv drenaj uygulanmasına rağmen klinik bulgusu, biyokimyasal enflamasyon belirteçleri veya radyolojik bulguları düzelmeyen hastalar "başarısız medikal tedavi" grubuna alındı (n=12). Demografik veriler (yaş, kilo, gravida, parite, kürtaj, defans/rebound varlığı, vajinal akıntı, servikal hareket hassasiyeti, ateş, hastanede kalış süresi), laboratuvar sonuçları [C-reaktif protein (CRP), prokalsitonin, beyaz küre sayısı, nötrofil sayısı, lenfosit sayısı, nötrofil-lenfosit oranı] ve hastaların hastaneye yatış günündeki radyolojik raporları (apse boyutu) hastane kayıtlarından alındı.

**Bulgular:** Medikal tedavinin başarısız olduğu grubun hastaneye yatış gününde servikal hareket hassasiyeti, CRP düzeyleri ve hastanede kalış süresi başarılı medikal tedavi grubundan daha yüksekti (tümü için $p<0,05$). CRP düzeyi, TOA'da medikal tedavi başarısını öngörmede tanısal yeterliliğe sahipti (AUC =0,71, p=0,03). Başvuru sırasında CRP seviyesi <144 mg/L olması %88,2 pozitif prediktif değere (PPV) sahiptir. Servikal hareket hassasiyetinin olmaması ile beraber CRP seviyesi <144 mg/L olması,

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**ABSTRACT**

The absence of cervical motion tenderness with CRP <144 mg/L had 100% PPV in prediction of the success of the medical treatment of TOA (AUC =0.77, p=0.006).

**Conclusion:** The absence of cervical motion tenderness and the CRP level on the day of hospitalization may predict the success of medical treatment in TOA.

**Keywords:** Cervical motion tenderness, CRP, tubo-ovarian abscess

**ÖZ**

TOA'da medikal tedavi başarısını tahmin etmek için %100 PPV'ye sahipti (AUC =0,77, p=0,006).

**Sonuç:** Hastaneye yatış gününde servikal hareket hassasiyeti olmaması ve CRP düzeyi TOA'da medikal tedavi başarısını öngörebilir.

**Anahtar Sözcükler:** Servikal hareket hassasiyeti, CRP, tubo-over apse

## Introduction

Tubo-ovarian abscess (TOA) is an inflammatory disease involving the fallopian tubes, ovaries, and in some patients, other adjacent pelvic organs (1). TOA is most often caused by the ascending progression of upper genital tract infections to the adnexa in sexually active women. TOA is one of the important causes of morbidity and mortality in gynecology. Sepsis and death secondary to TOA occurred in almost one out of every two patients during periods when antibiotherapy and interventional approaches could not be applied effectively (2). Today, TOA is a disease that can be treated only with antibiotic therapy in most patients. However, it causes a major cost due to long hospital stays. In addition, the prolongation of the hospitalization period undermines the patients' belief in treatment and reveals the possibility of refusal of the treatment by the patient. Surgical treatment of TOA provides the definitive solution in medical treatment-resistant patients. However, surgery in TOA is a challenging intervention due to the presence of adhesions in pelvis, risks of injuries to adjacent organs such as bowel and bladder, and possibility of salpingectomy, oophorectomy and even hysterectomy. It is necessary to avoid approaches that may impair the function of the genital system, especially in patients in the reproductive period.

Various hematological markers are used in the diagnosis and management of many diseases associated with inflammation and infection. Among them, white blood cell count (WBC) and C-reactive protein (CRP) are the most commonly used biomarkers. It has been found that procalcitonin (PCT) is also a useful marker for systemic inflammation and is superior to CRP for this purpose (3). A meta-analysis evaluating the prognostic functions of PCT and CRP reveals that the diagnostic accuracy of PCT is superior to CRP in patients hospitalized for suspected bacterial infection (4). In addition, it has been shown in recent years that neutrophil-to-lymphocyte ratio (NLR) can be used in the management of some inflammation-related diseases such as gastritis (5), appendicitis (6) and surgical site infection (7,8). There are studies in the literature, examining the relationship between NLR and TOA. In a study performed in terms of prediction of TOA diagnosis, preoperative NLR was found to be a highly successful marker in the performance analysis (9). In another study, the role of NLR was found useful in predicting medical treatment failure in TOA (10). There are only these two studies in the literature examining the relationship between NLR and TOA. Although NLR has been speculated as a marker with a high potential in both studies, the predictive value of NLR is still controversial.

In this study, we aimed to examine the role of hematological inflammation markers and clinical findings on the day of hospitalization in predicting medical treatment failure in patients with TOA.

## Methods

This retrospective cohort study was conducted with patients admitted to our hospital and hospitalized with the diagnosis of TOA between August 1, 2020 and July 1, 2021. Ethics committee approval was obtained for our study (approval number: 2021-08-170).

The diagnosis of TOA was made by the presence of a tubo-ovarian mass on ultrasound in patients with suspected pelvic inflammatory disease (PID). The diagnosis of PID was made clinically in sexually-active patients with pelvic or abdominal pain in the presence of cervical, uterine or adnexal tenderness. Additional signs and symptoms of PID werevaginal purulent discharge, high fever (>38.3 °C) and abnormal biochemical tests such as elevated CRP, PCT and/or WBC.

In our clinic, all patients diagnosed as having TOA are hospitalized and followed-up. All patients are treated with intravenous gentamicin and clindamycin in accordance with TOA management in the Centers for Disease Control and Prevention guideline (11). After the treatment is initiated, complete blood count, CRP and PCT examinations are performed every other day, and the size of the mass is followed daily by ultrasound.

The diagnostic criteria for the group considered as medical treatment failure were clinical findings, biochemical inflammation-related markers or radiological findings that did not improve despite treatment. Surgery or minimally-invasive drainage was performed in medical treatment failure group after at least 48 hours of antibiotic treatment. After intervention, antibiotherapy was continued in all patients until discharge. In this study, patients who did not receive an appropriate antibiotic therapy regimen, who left the hospital without completing their treatment, or whose diagnosis of TOA could not be confirmed during surgery were not included in the study.

Demographic data (age, weight, gravidity, parity, abortion, presence of abdominal guarding, rebound, vaginal discharge, cervical motion tenderness or fever, length of stay), laboratory results [CRP, PCT, WBC, neutrophil count (NEU), lymphocyte count, NLR] and radiological reports (abscess size) of the patients on the day of hospitalization were obtained from hospital records.

Finally, a total of 49 patients who met these inclusion and exclusion criteria and from whom all necessary information for the study could be obtained from the hospital records were enrolled into the study.

**Statistical Analysis**

In descriptive statistics, categorical variables of gravidity, parity, abortion, presence of abdominal guarding, rebound, vaginal discharge, cervical motion tenderness and fever were presented as frequency and percentage. Chi-square test was used for comparison of the categorical variables. Mann-Whitney U test was used to compare the continuous parameters among the successful medical treatment and medical treatment failure groups and the results were given as median (25-75$^{th}$ percentile). Correlations between parameters were tested with Spearman's test and the correlation coefficient (r) of 0.10-0.39 was interpreted as weak correlation and of 0.40-0.69 was interpreted as moderate correlation (12). Receiver operating characteristic analysis was performed for CRP level to predictt the success of medical treatment of TOA. The optimal cut-off values were selected using Youden's (13) index. Sensitivity, positive predictive value (PPV), specificity and negative predictive value (NPV) of the cervical motion tenderness and optimal cut-off value of CRP were calculated and reported. All statistical analyses were performed using SPSS 17 (SPSS Inc., Chicago, Illinois, USA) and p-value <0.05 was considered statistically significant.

## Results

Comparatively results of demographic, clinical and biochemical of the patients with TOA who had successful medical treatment (n=37) and those who had medical treatment failure (n=12) were given in Table 1. TOA groups were homogeneous for age, weight, gravidity, parity and abortion (p>0.05 for all). At the time of admission, cervical motion tenderness was present in 62.2% of the successful medical treatment TOA group while it was present in 100% of the medical treatment failure TOA group (p=0.01). CRP levels in the medical failure group at admission were higher than successful medical treatment group (158 vs 97 mg/dL; p<0.001). The length of stay of the medical failure group was longer than successful medical treatment group (12 vs 7 days; p=0.003).

The correlations between the parameters among patients with TOA are given in Table 2. Weak positive correlations were found between abscess size, CRP level and length of stay while there was moderate positive correlation between CRP level and length of stay (r=0.31, p=0.04; r=0.34, p=0.03; r=0.40, p=0.004, respectively).

It was determined that CRP level had diagnostic adequacy for prediction of the success of the medical treatment of TOA (AUC =0.71, p=0.03). At the time of admission, CRP level <144 mg/L had 88.2% PPV. The absence of cervical motion tenderness with CRP <144 mg/L had 100% PPV for prediction of the success of the medical treatment of TOA (AUC =0.77, p=0.006) (Table 3).

## Discussion

Our study revealed that the absence of cervical motion tenderness and CRP levels below 144 mg/L at the time of admission might predict the success of the medical treatment in TOA.

Treatment modalities in TOA are broad-spectrum antibiotic therapy, invasive intervention such as drainage or surgery, or a combination of both. Broad-spectrum antibiotics are sufficient in approximately three-quarters of patients (14). Even if a surgical intervention is performed, it is often preferred to use antibiotics before and after the procedure since antibiotic therapy is an important part of the treatment. Predicting medical treatment failure in patients with TOA can shorten the treatment period, reduce the cost of hospitalization and possible complications with an early intervention. There are studies conducted in this purpose in the literature. In previous studies, the relationship between age, presence of intrauterine device, abscess size, WBC and CRP levels and medical treatment failure in TOA were examined (10,15-17). In the study of Farid et al. (15), it was stated that high WBC count in large abscesses could predict the medical treatment failure. In a study, Greenstein et al. (17) determined that in addition to these two predictors, age and parity were also associated with the medical treatment failure in TOA. In another study, the size of the tubo-ovarian mass was investigated as a predictor and the mean abscess diameter was found larger in patients with TOA who underwent surgery (18). However there were different cut-off values for abscess size reported in literature (19-21). Therefore, there was no consensus in this regard. Güngördük et al. (16), stated that CRP was significantly higher in the group with TOA that did not respond to the medical treatment. Erenel et al. (18) found that the initial serum PCT levels in patients with TOA were significantly higher compared to patients with PID without TOA. In this study, it was argued that PCT provided a better differentiation than CRP between PID patients with and without TOA. In another study aiming to predict the progression to surgical treatment in patients with TOA, no significant difference was found in terms of PCT levels between successful medicaltre treatment and medical treatment failure groups (22). Finally, in a recent study by Alay et al. (10), age, WBC, NEU, and NLR were found to be independent risk factors for the medical treatment failure in TOA. In this study, it was speculated that especially NLR might be a promising biomarker in predicting the medical response in TOA. In this study, CRP levels were found higher in the medical treatment failure group.

In our study, it was determined that the absence of cervical motion tenderness (sensitivity 37.8%, PPV 100%, specificity 100% and NPV 34.3%) and lower CRP levels (for cut-off value of 144 mg/L, sensitivity 81.1%, PPV 88.2%, specificity 66.7%,

**Table 1.** Demographic, clinical and biochemical results of the patients with TOA

| | Successful medical treatment group (n=37) | Medical treatment failure group (n=12) | p value |
|---|---|---|---|
| Age (years) | 38 (35-43) | 42 (32-47) | 0.37 |
| Weight (kg) | 65 (61-75) | 70 (65-84) | 0.24 |
| Gravidity (n) | 3 (2-4) | 2 (2-4) | 0.71 |
| Parity (n) | 0 (0-2) | 1 (0-1) | 0.85 |
| Abortion (n) | 2 (1-3) | 2 (1-3) | 0.86 |
| Presence of guarding (n, %) | 12 (32.4%) | 7 (58.3%) | 0.17 |
| Presence of rebound (n, %) | 9 (24.3%) | 2 (16.7%) | 0.71 |
| Presence of vaginal discharge (n, %) | 6 (16.2%) | 4 (33.3%) | 0.23 |
| Presence of cervical motion tenderness (n, %) | 23 (62.2%) | 12 (100%) | **0.01** |
| Presence of fever (n, %) | 2 (5.4%) | 3 (25.0%) | 0.09 |
| Abscess size (cm) | 5.2 (4.0-7.0) | 6.3 (5.1-7.9) | 0.25 |
| Length of stay (days) | 7 (4-8) | 12 (10-16) | **<0.001** |
| CRP (mg/L) | 97 (46-142) | 158 (90-219) | **0.03** |
| PCT (ng/mL) | 0.12 (0.04-0.66) | 0.31 (0.08-0.75) | 0.23 |
| WBC ($10^9$/L) | 12.6 (9.2-17.5) | 13.4 (12.1-18.7) | 0.24 |
| NEU ($10^9$/L) | 9.7 (6.7-14.4) | 9.9 (9.0-15.1) | 0.52 |
| LYM ($10^9$/L) | 1.6 (1.4-2.2) | 2.1 (1.2-2.7) | 0.29 |
| NLR | 6.0 (4.6-8.2) | 4.5 (3.7-9.4) | 0.55 |

CRP: C-reactive protein, PCT: Procalcitonin, WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, NLR: Neutrophil lymphocyte ratio

**Table 2.** Correlations (r) between parameters among patients with TOA

| | Age | Abscess size | Length of stay | CRP | PCT | WBC | NEU | LYM | NLR |
|---|---|---|---|---|---|---|---|---|---|
| **Age** | 1 | -0.04 | 0.30* | -0.02 | 0.17 | -0.02 | -0.01 | -0.15 | 0.06 |
| **Abscess size** | | 1 | 0.31* | 0.34* | 0.07 | -0.01 | 0.01 | -0.04 | 0.04 |
| **Length of stay** | | | 1 | 0.40** | 0.21 | 0.13 | 0.11 | -0.12 | 0.17 |
| **CRP** | | | | 1 | 0.52** | 0.41** | 0.42** | -0.20 | 0.51** |
| **PCT** | | | | | 1 | 0.21 | 0.26 | -0.40** | 0.56** |
| **WBC** | | | | | | 1 | 0.97** | 0.29* | 046** |
| **NEU** | | | | | | | 1 | 0.13 | 0.62** |
| **LYM** | | | | | | | | 1 | -0.63** |
| **NLR** | | | | | | | | | 1 |

*p<0.05, **p<0.01
CRP: C-reactive protein, PCT: Procalcitonin, WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, NLR: Neutrophil lymphocyte ratio

**Table 3.** Diagnostic performances of cervical motion tenderness and CRP level in prediction of the success of medical treatment of TOA

| | Cut-off | Sensitivity | PPV | Specificity | NPV |
|---|---|---|---|---|---|
| Absence of cervical motion tenderness | - | 37.8% | 100% | 100% | 34.3% |
| CRP (mg/L) | <144 | 81.1% | 88.2% | 66.7% | 53.3% |
| Absence of cervical motion tenderness with CRP <144 mg/L | - | 32.4% | 100% | 100% | 32.4% |

PPV: Positive predictive value, NPV: Negative predictive value

and NPV 53.3%) might have a role in predicting the medical treatment success in TOA. We could not find any significant differences in WBC, NEU, NLR or PCT among the groups.

### Study Limitations

There are some strengths and limitations of our study. To our knowledge, this is the second study in the literature to investigate the role of NLR in predicting the success of medical treatment in TOA. Unlike previous studies, it has been shown that the absence of cervical motion tenderness may be associated with response to treatment. However, cervical motion tenderness is a subjective finding. Therefore, this is one of the limitations of our study. Also, the small sample size reduces the generalizability of the results.

## Conclusion

The absence of cervical motion tenderness and CRP level on the day of hospitalization may predict the success of medical treatment in TOA. Further studies are needed to clarify the results obtained in order to predict the treatment response in TOA.

### Ethics

**Ethics Committee Approval:** Ethics committee approval was obtained for our study (approval number: 2021-08-170).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: F.A., C.T., Concept: F.A., Design: F.A., Data Collection or Processing: C.T., H.Ü., Analysis or Interpretation: E.V., Literature Search: F.A., Writing: F.A., C.T., E.V.

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

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Original Article

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# Analgesic Efficacy of Ibuprofen in Dysmenorrhea

## Dismenorede İbuprofen'in Analjezik Etkinliği

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## ABSTRACT

**Objective:** Non-steroidal anti-inflammatory drugs (NSAIDs) are used routinely and as first choice in the analgesic treatment of abdominal pain caused by primary dysmenorrhea (PD). In our study, we aimed to compare the analgesic efficacy of 400 mg and 800 mg ibuprofen doses administered intravenously (iv) in the treatment of patients presenting with abdominal pain due to PD.

**Methods:** The study was conducted in emergency department over a period of 4 months in a prospective, randomized, controlled and single-blind design. Females aged between 18-50 years were included in the study. The patients were randomly divided into two groups as those who received ibuprofen 400 mg and those who received 800 mg. In these two groups, the pain scores of the patients at 0, 30 and 60 min were determined and analyzed using the 10-unit Numeric Rating Scale (NRS).

**Results:** A total of 54 patients, 27 in each group were included in the study. Age, weight and body mass index parameters of the groups were statistically similar. There was no statistically significant difference between the two groups in terms of the degree of pain at admission and at the 30$^{th}$-60$^{th}$ min of follow-up. In the 400 mg and 800 mg treatment groups, the NRS score differences between 0 and30 min periods [median [interquartile range (IQR): 4 (3-5) and 4 (3-4); p=0.224] and between 0 and 60 min periods [median (IQR): 4 (3-5) and 4 (3-4); p=0.224] were statistically similar. There was no difference between the two groups in terms of need for rescue medication and side effects.

**Conclusion:** Similar efficacy is observed in reducing pain intensity between 400 mg and 800 mg doses of iv ibuprofen. According to these findings, it can be concluded that 400 mg of ibuprofen

## ÖZ

**Amaç:** Non-steroid anti-enflamatuvar ilaçlar (NSAİİ) primer dismenorenin (PD) neden olduğu karın ağrısının tedavisinde rutinde ilk tercih olarak kullanılmaktadır. Çalışmamızda PD nedeniyle karın ağrısı ile başvuran hastaların tedavisinde intravenöz (i.v.) olarak uygulanan 400 mg ve 800 mg ibuprofen dozlarının analjezik etkinliğini karşılaştırmayı amaçladık.

**Yöntemler:** Çalışma acil serviste, ileriye dönük, randomize, kontrollü ve tek kör tasarım ile 4 aylık bir süre boyunca yürütüldü. Çalışmaya 18-50 yaş arası kadınlar dahil edildi. Hastalar randomize olarak uygulanan ibuprofen dozuna göre 400 mg ve 800 mg i.v. olmak üzere iki gruba ayrıldı. Bu iki gruptaki hastaların 0, 30 ve 60 dakikadaki ağrı skorları belirlendi ve Numerik Rating Skala (NRS) kullanılarak analiz edildi.

**Bulgular:** Her grupta 27 olmak üzere toplam 54 hasta çalışmaya dahil edildi. Grupların yaş, kilo ve vücut kitle indeksi parametreleri arasında istatistiksel olarak fark yoktu. İki grup arasında başvurudaki ve 30-60. dakikalardaki ağrı dereceleri açısından istatistiksel olarak anlamlı fark yoktu. Dört yüz mg ve 800 mg tedavi gruplarında, hem 0-30 dakikalık dönem NRS farklılıkları [medyan (IQR): 4 (3-5) ve 4 (3-4); p=0,224] hem de 0-60 dakikalık dönem NRS farklılıkları [medyan (IQR): 4 [3-5] ve 4 (3-4); p=0,224] istatistiksel olarak benzerdi. Kurtarma ilacı ihtiyacı ve yan etkiler açısından iki grup arasında fark yoktu.

**Sonuç:** Ağrı yoğunluğunu azaltmada 400 mg ve 800 mg i.v. ibuprofen dozlarının etkinliklerinin benzer olduğu gözlendi. Bu bulgulara göre PD'li hastalarda karın ağrısı tedavisinde 400 mg ibuprofen i.v. preparatının 800 mg yerine tercih edilebileceği söylenebilir.

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**ABSTRACT**

IV preparation can be preferred over 800 mg in the treatment of abdominal pain in patients with PD.

**Keywords:** Abdominal pain, ibuprofen, intravenous, Numeric Rating Scale, primary dysmenorrhea

**ÖZ**

**Anahtar Sözcükler:** Karın ağrısı, ibuprofen, intravenöz, Numerik Rating Skala, primer dismenore

## Introduction

Dysmenorrhea is a gynecological problem accompanied by painful cramps during menstruation. It affects more than 50% of women during the menstrual period. In addition, there are publications stating that it affects more than 90% of women between the ages of 18-45 (1). In addition, it is known that abdominal pain due to dysmenorrhea is a serious burden in emergency services. Dysmenorrhea is classified as primary and secondary. Primary dysmenorrhea (PD) is a type of dysmenorrhea that occurs without underlying pelvic pathology. It is known that the strong vasoconstrictive and myometrium stimulating effect of prostaglandin-F2 alpha is responsible for the current pathogenesis of PD. NSAIDs suppress the activity of the cyclooxygenase-2 (COX-2) enzyme, thereby reducing cyclic endoperoxide production and prostaglandin levels, contributing to patients' analgesia and comfort (2). Based on these mechanisms, NSAIDs have gained a wide place in the treatment of PD, and it is known that NSAIDs are the preferred drug group in dysmenorrhea complaints (3).

The primary mechanism of action of ibuprofen from the NSAID drug group is through the inhibition of prostaglandin precursors. After physiological and pathological stimulation, membrane phospholipids secrete arachidonic acid in conjunction with the phospholipase A2 enzyme. Arachidonic acid then switches to one of three different enzymatic pathways: cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP450) (4). The COX route is an important factor for the current stated uses of ibuprofen. There are three different isoforms in the COX pathway: COX-1 (PGH synthase), COX-2 and COX-3. Inhibition of the COX-1 and COX-2 pathways reduces the release of prostaglandin precursors, which in turn reduces the severity of the cellular response to pathological and physiological stimuli. Non-selective NSAIDs such as ibuprofen show their analgesic properties by this mechanism (5).

The 400 mg and 800 mg intravenous (IV) forms of ibuprofen are approved for use in PD. However, no study was found comparing the analgesic efficacy of 400 mg and 800 mg IV doses of ibuprofen. The aim of this study was to compare the analgesic efficacy of 400 and 800 mg IV doses of ibuprofen in the control of moderate and severe pain in PD.

## Methods

### Settings and Design

This study was conducted in the Emergency Clinic of Ankara Bilkent City Hospital between 01.05.2021 and 31.08.2021 according to a prospective, randomized, controlled and single-blind research model. Approval for the study was obtained from the Clinical Research Ethics Committee of Ankara Bilkent City Hospital (date/number: 14.04.2021/E1-21-1609). Informed consent was obtained from all patients.

### Participants and Definitions

Patients who suffered from recurrent abdominal pain occurring during the menstrual cycle, with a diagnosis of PD were included in the study. Those who were hemodynamically stable and who volunteered to participate in the study were included. Other inclusion criteria were; patients with regular menstrual cycles with current pain "similar to pain in previous cycles", between the ages of 18-50, at pain score of baseline Numeric Rating Scale (NRS) ≥5. Exclusion criteria were; patients who were suspected or diagnosed with acute medical/surgical illness or pregnancy. Other exclusion criteria were: drug allergy to the subject of the study, and contraindications for the use of ibuprofen (such as acute renal failure, recent bypass surgery, liver failure, etc.), patients who used any analgesic drug in the last 6 hours. Mentally retarded or uncooperative subjects with hearing and/or visual impairments or any underlying organic neurological disorders were also excluded from the study. The population of the study consisted of female patients who presented to the emergency department with the complaint of "abdominal pain during the menstrual cycle", and the sample sample consisted of patients who met the criteria for participation in the research in the specified population. The pain scoring system utilized was NRS (Numeric Rating Scale), which is a numerically graded visual analog scale. This 11-point numerical scale ranges from "0" representing "no pain" to "10" representing "worst pain imaginable" (Figure 1). Body-mass index was calculated using the weight and height values of the patients (weight/height squared; kg/m$^2$) and added to the analysis.

### Intervention

The patient who met the inclusion criteria of our study was taken to a reserved examination room. Detailed information about the drugs used in the study along with the list of drugs that can be administered to the patients was given to the patients by the doctor there, and an informed consent form was signed. The initial pain score before the procedure was determined and recorded using the 10-unit NRS. NRS markings on the case report forms were made by the patient before and during the procedure, regardless of the previous marking. The patient's file numbers, height, weight, age, gender, application date and time were recorded along with the drug number applied on the same form. Oxygen saturation, blood pressure, rhythm


**Figure 1.** Numeric rating scale

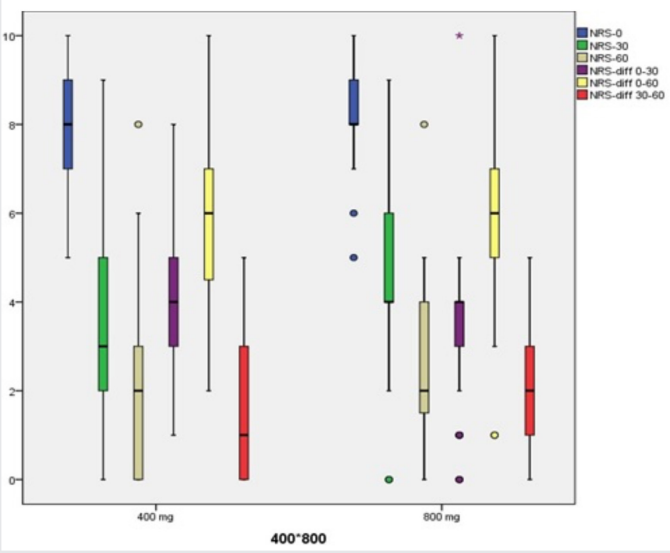


**Figure 2.** NRS scores and differences in two groups
*NRS: Numeric Rating Scale*

and body temperature were monitored during the procedure. NRS scores at 30 and 60 minutes after randomization were evaluated and recorded. Rescue treatment protocol was started for patients whose pain score did not decrease or increased at 30 minutes, or whose NRS score was >3 at 60 minutes. As salvage treatment, tramadol hydrochloride was planned as 100 mg IV as a 30-minute infusion in 500 mL physiological saline.

Randomization was carried out using the closed envelope method. Group names of 400 mg and 800 mg were written in a total of 54 sealed envelopes, 27 for each group. The baseline NRS score was determined for patients who met the criteria and were accepted into the study, and randomization was performed for patients with this value ≥5. For this purpose, 1 sealed envelope was randomly selected and administered to the patient in 150 mL of 0.9% NaCl IV ibuprofen at the dose written in it for 10 minutes. At this stage, only the patient was blinded to the drug group. Researchers and other healthcare professionals were not blinded to the practice.

### Outcomes

As a result, in the case report forms, age, gender, presence of chronic disease, vital signs, admission complaint, onset time of the complaint, pain localization, pain spread, previous analgesic use, if used, when, the treatment given, at 0, 30 and 60 minutes. NRS pain score, whether or not rescue medication was used and whether there were any side effects were recorded. These data were analyzed comparatively between the two groups, considering the pain scores at 30-60 minutes and the degree of pain score reduction in the 0-30 and 0-60 minute periods as primary outcomes, the need for rescue analgesics and drug side effects as secondary outcomes.

### Statistical Analysis

IBM SPSS.16 for Windows (SPSS Inc., Chicago, Ill., USA) program was used for statistical analysis of the study. In the study, Pearson chi-square and Fisher's Exact tests were used for ratio comparisons of categorical data. Distribution analysis of continuous data was made with the Shapiro-Wilk test, comparisons of medians between two groups of non-normally distributed data were made with Mann-Whitney U test, and mean comparisons between two independent groups in data with normal distribution were made with Independent Samples t-test. Statistical significance was generally used at the $p<0.05$ level.

For the study, a sample size analysis was carried out using the data in the study of Ayan et al. (6). In this analysis, it was calculated that at least 26 patients should be included in each group based on the initial VAS score standard deviation of 16 mm, 95% power, and 5% Type 1 error.

## Results

A total of 54 female patients were included in the study, 27 patients (50%) in both groups (400 mg and 800 mg). No patients were excluded from the study after randomization, and all patients received the planned treatment and follow-up. Analyzes were performed on 54 (100%) patients. The age distribution of the patients in the two groups was similar (median: 25 vs 24; p=0.521). Weight, body mass index, family history, pain onset time, and previous analgesic use were also found to be homogeneously distributed in both groups (Table 1). Quadrants where abdominal pain is localized are also shown in Table 1. In the patient histories, it was determined that pain was observed regularly in every cycle in 47 (87.0%) of the patients.

The degree of pain at admission (NRS-0) and 30-60 at follow-up. There was no statistically significant difference between the two groups in terms of pain degree (NRS-30 and NRS-60) in minutes (Table 2). Although the mean of NRS-30 was higher in the "800 mg" group (mean ± standard deviation [95% confidence interval: 4.7±2.2 (3.8-5.5) vs 3.6±2.6 (2.6) -4.6); p=0.114], this difference was not statistically significant (Table 2). Figure 2 shows the box-plot graph of these three pain levels.

**Table 1.** Demographics and clinical features

| Parameters | | Ibuprofen dose 400 mg n=27 (50%) Median (IQR) | 800 mg n=27 (50%) Median (IQR) | p-value |
|---|---|---|---|---|
| Age (year) | | 25 (22-28) | 24 (21-27) | 0.521* |
| Weight (kg) | | 52 (50-60) | 56 (53-60) | 0.327* |
| BMI | | 21.56 (19.48-23.31) | 20,45 (19.57-21.01) | 0.411* |
| Dose for per kg | | 7.69 (6.67-8) | 14,29 (13.33-15.09) | <0,001* |
| First menstrual cycle (day) | | 13 (13-14) | 14 (14-14) | 0.028* |
| Complaint time (hour) | | 5 (2-10) | 6 (3-8) | 0.917* |
| Family history- **n (%)** | | 6 (33.3) | 11 (61.1) | 0.095† |
| Pain in all cycle- **n (%)** | | 21 (77.8) | 26 (96.3) | 0.100‡ |
| Pain quadrant **n (%)** | Diffuse | 1 (3.7) | 4 (14.8) | - |
| | Suprapubic | 21 (77.8) | 19 (70.4) | |
| | Right lower | 2 (7.4) | 1 (3.7) | |
| | Left lower | 3 (11.1) | 3 (11.1) | |
| Agitation- **n (%)** | | 8 (29.6) | 17 (63.0) | 0.014† |
| Prior analgesia- **n (%)** | | 1 (3.7) | 5 (18.5) | 0.192‡ |
| Prior analgesia (hours ago) | | 24 (24-24) | 8 (8-8) | 0.206* |

*Mann-Whitney U test
†Pearson chi-squared test
‡Fisher's Exact test
IQR: Interquartile range, BMI: Body mass index

**Table 2.** NRS and other main outcomes

| Parameters | Ibuprofen dose 400 mg Median (IQR) | 800 mg Median (IQR) | p-value |
|---|---|---|---|
| NRS0 | 8 (7-9) | 8 (8-9) | 0.224* |
| NRS30- **mean ± SD (95% CI)** | 3.6±2.6 (2.6-4.6) | 4.7±2.2 (3.8-5.5) | 0.114† |
| NRS60 | 2 (0-3) | 2 (1-4) | 0.310* |
| Rescue medicine- **n (%)** | 2 (7.4) | 1 (3.7) | 1.000‡ |
| Side effect- **n (%)** | 1 (3.7) | 0 (0) | 1.000‡ |

*Mann-Whitney U test
†Independent Samples t-test- mean ± SD (95% confidence interval)
‡Fisher's Exact test
IQR: Interquartile range, NRS0: Initial Numeric Rating Scale, NRS30: Numeric Rating Scale (30$^{th}$ minute), NRS60: Numeric Rating Scale (60$^{th}$ minute)

**Table 3.** Difference in NRS (30$^{th}$ and 60$^{th}$ minutes)

| Parameters | Ibuprofen dose 400 mg | 800 mg | p-value |
|---|---|---|---|
| NRS-diff 0-30, **median (IQR)** | 4 (3-5) | 4 (3-4) | 0.224* |
| NRS-diff 0-60, **mean ± SD (95% CI)** | 5.8±1.8 (2.6-4.6) | 5.8±2.2 (3.8-5.5) | 0.114† |
| NRS-diff 30-60, **median (IQR)** | 1 (0-3) | 2 (1-3) | 0.137* |

*Mann-Whitney U test
†Independent Samples t-test- mean ± SD (95% confidence interval)
NRS: Numeric Rating Scale, NRS-diff: NRS difference, IQR: Interquartile range, SD: Standard deviation, CI: Confidence interval

The need for rescue medication was seen in 3 patients in all patients, the rate here being 7.4% in the first group and 3.7% in the second group (p=1,000). Adverse effects were detected as "nausea-vomiting" in only 1 patient (3.7%) in the 400 mg group (Table 2).

In addition, changes in the degree of pain were also analyzed. Differences in NRS at 0-30 minutes were similar between the 400 mg and 800 mg groups [median (IQR): 4 (3-5) vs 4 (3-4); p=224], respectively. Similarly, the NRS differences between 0-60 minutes [respectively, median (IQR): 5.8±1.8 (2.6-4.6) vs. 5.8±2.2 (3.8-5.5); p=114] were also found to be similar. Although the median of the 30-60 minute difference in the 800 mg" group was high [median (IQR): 1 (0-3) vs 2 (1-3); p=137], this difference was not statistically significant (Table 3). These differences are also expressed graphically (Figure 2).

## Discussion

Dysmenorrhea is a common gynecological problem consisting of painful cramps accompanying menstruation and is classified as PD when there is no underlying abnormality. Studies have shown that women with dysmenorrhea have high levels of prostaglandins, which play a role in the etiology of pain. NSAIDs provide analgesic effects by suppressing prostaglandin synthesis (7). In this study, the analgesic efficacy of 400 mg and 800 mg IV doses of ibuprofen, which is a drug from the NSAID group, which is frequently used in dysmenorrhea, was found to be similar. As far as we could detect from the literature, this study is the first to compare the effectiveness of different doses of ibuprofen in dysmenorrhea pain.

The prospective and randomized design of the study is one of its strengths, and the fact that the participants are blind to drug doses is another factor that increases reliability. However, the fact that researchers and healthcare personnel are not blind should be considered a handicap, on the contrary. Since there is no data on the characteristics of the participants such as whether they are virgins, previous sexual activities, gravida-parity and presence of intrauterine device, the results of the study cannot be customized to any patient group related to these conditions.

It has been proven that various factors such as early menarche age, increased menstrual bleeding, alcohol and tobacco use, low socioeconomic status, obesity, depression, nulliparity, irregular menstrual cycle, long menstruation duration, and family history of dysmenorrhea increase the risk of dysmenorrhea (8-10). First of all, the age at which the patients included in the study at first menstruation and menstruation with regular cycles were consistent with the literature. There was a family history of dysmenorrhea in 17 of our patients. Although this is an important risk factor for dysmonea, it was seen at a rate similar to other studies (10). In this study, the median body-mass index was 20.56 (19.53-22.31); Similar values are also mentioned in the study of Camlibel et al. (2) conditions seen in women during the menstrual cycle include mood disorders such as anxiety, depression, irritability and irritability (10). Agitation and anxiety were present in 46.3% of the patients included in our study. Although the relationship between anxiety and pain has been evaluated in different diseases, this subject is open to study in dysmenorrhea cases. Studies have also shown that women younger than 25 are more likely to have PD, and its prevalence decreases with increasing age (10). In our study, the mean age of the patients was calculated similar to the existing data for both groups. In the literature, it has been reported that pain levels are moderate and severe in the significant majority of PD patients (11-13). In the results we found in our study, the pain levels of the patients at the time of admission were moderate to high.

Although the pathophysiology of PD is not fully clarified, it is thought that increased prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) levels in the etiology increase the sensitivity of myometrial contractions, uterine ischemia and pain fibers (9,14,15). For this reason, NSAIDs act as a building block in the treatment of PD, as they suppress prostaglandin synthesis by inhibition of COX enzyme, and ibuprofen and many other NSAIDs are primarily preferred among treatment options (14,16).

There are many studies with ibuprofen in the treatment of PD. However, most of these studies are studies comparing ibuprofen versus another agent. In a study, ibuprofen's 400 mg form versus placebo and 64 mg doses of proxifen were compared, and it was stated that the analgesic efficacy of ibuprofen was superior (17). In another study in which 33 patients were evaluated for 3 months, it was shown that ibuprofen was superior to the other two agents in the treatment of ibuprofen 200 mg, aspirin 425 mg and placebo (13). In another study involving 55 female patients, it was shown that the analgesic efficacy of ibuprofen 400 mg dose was superior to proxifen hydrochloride and placebo (18).

In a study conducted in Spain, it was reported that women with dysmenorrhea used analgesics such as NSAIDs, paracetamol, and antispasmodics due to existing pain, and most of them used mefenamic acid, ibuprofen, paracetamol, ketoprofen, and diclofenac (19). In addition, in another study, it was seen that the primary preferences of most of the patients were ibuprofen and diclofenac (20) Although all these analgesic drugs used in the treatment of dysmenorrhea were effective in reducing the degree of pain regardless of the frequency of use, dose range and administration route, ketoprofen and other NSAIDs were more effective than paracetamol, but there was no statistically significant difference between NSAIDs (10).

Ibuprofen and naproxen, which are arylpropionic acid derivatives, are frequently preferred in the treatment of dysmenorrhea and have less side-effect profiles than other NSAIDs. It has been shown that 80% of patients treated with ibuprofen and naproxen provide almost perfect relief compared to placebo (21). Zhang et al. (22) as a result of scanning 56 studies in dysmenorrhea; It was stated that ibuprofen, naproxen, aspirin and mefenamic acid were superior to placebo. In addition, it has been shown that naproxen and ibuprofen have less need for rescue medication, less restriction of daily life, and adaptation problems to work or school life, and that the side-effect profile of ibuprofen has a lower side-effect profile (22). In a meta-analysis to evaluate the

efficacy and safety of naproxen, ibuprofen, diclofenac, aspirin, and ketoprofen, it was stated that diclofenac and ibuprofen were more effective than others in their analgesic efficacy in PD, and ketoprofen and ibuprofen were the safest agents in the safety evaluation (23). In line with the current studies and meta-analyses, ibuprofen stands out among other NSAIDs in terms of its effectiveness and safety.

Comparing the analgesic efficacy of ibuprofen 400 and 800 mg in the treatment of postoperative pain, 800 mg of ibuprofen was used in orthopedic trauma patients, 800 mg of ibuprofen was used after hip replacement surgery, and ibuprofen 800 mg iv. There are studies in the literature in which the effectiveness of the form is superior (24-26). A study comparing the analgesic efficacy of 400 and 800 mg doses of ibuprofen in studies with PD could not be found in the literature. According to the information in the prospectus, it is recommended to use the parenteral form of ibuprofen at a dose of 200-400 mg for antipyretic purposes, and 400-800 mg as an analgesic. In this study, 400-800 mg doses of ibuprofen were selected for moderate-to-severe pain pattern. The degrees of NRS reduction were found to be similar in the 0-30 and 0-60 minute periods of their analgesic effects; with these data, it can be thought that the 400 mg dose should be chosen as a priority. It is recommended that these doses be repeated every 4-6 hours. In this study, there is no data on the processes after the 60th minute due to the short follow-up times in the emergency department. However, since this study was conducted in the group of patients who applied to the emergency department, the importance of the first hour in pain treatment seems obvious in these conditions. Maintenance oral treatments that will be offered to the patient at discharge may help achieve analgesia goals within days; however, these goals are not the subject of this study.

### Study Limitations

The most important limitation of the study is that the researchers were not blinded in the study design. In addition, although the number of cases was determined according to the sample size analysis, more reliable results can be obtained with higher patient numbers. NRS score was used for pain grading due to the advantage of easy use, and we can say that more sensitive results can be obtained with the visual analog scale. The fact that the pain was not followed up from the 60$^{th}$ minute can be counted as a separate limitation.

## Conclusion

According to the results of the study, ibuprofen 400 mg and 800 mg IV forms have similar analgesic efficacy in the treatment of PD. Although no serious side effects related to ibuprofen were observed in this study, it would be more rational to use a similarly effective 400 mg IV dose. Considering that ibuprofen is used very frequently in the region where this study was conducted, we think that it will be possible to reflect these results in practice at a high rate. Comparing these doses in different indications may be important to further clarify the issue.

### Ethics

**Ethics Committee Approval:** Approval for the study was obtained from the Clinical Research Ethics Committee of Ankara Bilkent City Hospital (date/number: 14.04.2021/E1-21-1609).

**Informed Consent:** Obtained.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

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

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# Cerebroplacental Ratio During the Third Trimester of Pregnancy: A Prospective Case-Control Study

## Gebeliğin Üçüncü Trimesterinde Maternal Demir Eksikliği Anemisi ve Şiddetinin Serebroplasental Oran ile İlişkisi

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## ABSTRACT

**Objective:** The aim of this study is to evaluate iron deficiency anemia and its severity in relation to the cerebroplacental ratio (CPR) in the third trimester of pregnancy.

**Methods:** The research was planned as a prospective study. The World Health Organization (WHO) recommends that hemoglobin (Hb) level should remain above 11.0 g/dL during pregnancy. The WHO guidelines define Hb values between 10 and 10.9 g/dL as mild anemia, and between 7 and 9.9 g/dL as moderate anemia. The CPR was calculated by dividing the middle cerebral artery pulsatility index (MCA PI) by the umbilical artery (UA) PI.

**Results:** Of the 108 pregnant women in this study, 40 were grouped as moderately anemic, 34 as mild anemic, and 34 as healthy. Demographic characteristics were similar between the groups. MCA PI values were 1.89±0.34 in the moderate anemia group, 1.63±0.32 in the mild anemia group, and 1.57±0.39 in the control group, and there was a significant difference among the groups (p<0.001). UA PI values were 0.92±0.18 in the moderate anemia group, 1.01±0.15 in the mild anemia group, and 1.01±0.14 in the control group (p=0.013). While the MCA resistance index (RI) values were similar between the groups (p=0.836), there was a significant difference between the groups in terms of UA RI (p=0.042). CPR PI values were 2.11±0.43 in the moderate anemia group, 1.62±0.22 in the mild anemia group, and 1.56±0.4 in the control group (p<0.001).

## ÖZ

**Amaç:** Bu çalışmanın amacı, gebeliğin üçüncü trimesterinde demir eksikliği anemisi ve şiddeti ile serebroplasental oran (CPR) ilişkisini değerlendirmektir.

**Yöntemler:** Araştırma prospektif olarak planlanmıştır. Dünya Sağlık Örgütü (DSÖ), hamilelik sırasında hemoglobin (Hb) düzeylerinin 11,0 g/dL'nin üzerinde kalmasını önermektedir. DSÖ kılavuzları, 10 ila 10,9 g/dL arasındaki Hb değerlerini hafif anemi, 7 ila 9,9 g/dL arasındaki değerleri orta derecede anemi olarak tanımlar. CPR, orta serebral arter pulsatilite indeksinin (MCA PI) umbilikal arter (UA) PI'ya bölünmesi ile hesaplandı.

**Bulgular:** Bu çalışmadaki 108 gebenin 40'ı orta derecede anemik, 34'ü hafif anemik ve 34'ü sağlıklı olarak gruplandı. Demografik özellikler gruplar arasında benzerdi. Orta dereceli anemi grubunda MCA PI 1,89±0,34, hafif anemi grubunda 1,63±0,32, kontrol grubunda 1,57±0,39 idi ve gruplar arasında anlamlı fark vardı (p<0,001). UA PI değerleri orta dereceli anemi grubunda 0,92±0,18, hafif anemi grubunda 1,01±0,15 ve kontrol grubunda 1,01±0,14 idi (p=0,013). Gruplar arasında MCA direnç indeksi (RI) değerleri benzer iken (p=0,836) UA RI'da gruplar arasında anlamlı fark vardı (p=0,042). CPR PI değerleri orta dereceli anemi grubunda 2,11±0,43, hafif anemi grubunda 1,62±0,22 ve kontrol grubunda 1,56±0,4 idi (p<0,001).

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**Conclusion:** Our results suggested that MCA PI, UA PI, UA RI, and CPR PI were altered in the presence of iron deficiency anemia in the third trimester of pregnancy.

**Keywords:** Iron deficiency anemia, third trimester, cerebroplacental ratio, CPR

**Sonuç:** Sonuçlarımız, gebeliğin üçüncü trimesterinde demir eksikliği anemisi varlığında MCA PI, UA PI, UA RI ve CPR PI'nın değiştiğini göstermektedir.

**Anahtar Sözcükler:** Demir eksikliği anemisi, üçüncü trimester, serebroplasental oran, CPR

## Introduction

Although treatable, iron deficiency anemia is the most widespread nutritional disorder worldwide affecting approximately 40% of pregnancies (1,2). Hemodilution causes anemia in pregnancy after the plasma volume increases beginning in the first trimester of pregnancy. The World Health Organization recommends that hemoglobin (Hb) levels are maintained above 11.0 g/dL in pregnancy and do not fall below 10.5 g/dL in the second trimester (3). A mother requires approximately 1130 mg of total iron in the antepartum and postpartum periods (4). This value changes over time from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester (5).

Anemia in pregnancy can cause severe maternal and perinatal complications. Anemia increases the risks of preterm birth and low birth weight (6). Fetal growth accelerates in the third trimester, increasing the fetal need for iron. If anemia is present, the fetus receives less oxygen transfer causing hypoxemia, which may result in a restructuring of the blood flow in the fetus. Therefore, fetal brain blood flow increases because of a decreased resistance to flow in the fetal middle cerebral artery (MCA) and increased resistance in the umbilical artery (UA) (7,8). Monitoring fetal blood flow using a Doppler ultrasound has significantly improved the perinatal morbidity and mortality rates of pregnancies affected by fetal growth restriction (FGR) caused by this change in blood flow. Furthermore, abnormal Doppler findings in uncomplicated pregnancies without FGR might be associated with adverse perinatal outcomes. In particular, the cerebroplacental ratio (CPR), defined as the MCA pulsatility index (PI)/UA PI, may serve as a reliable indicator of these adverse outcomes (9,10). It is hypothesized that FGR may occur due to insufficient circulation and oxygenation due to maternal iron deficiency anemia in the early third trimester. In order to prevent intrauterine growth retardation in fetuses due to anemia , Doppler can be used in addition to blood tests performed during follow-up. Hence, in the current study, we aimed to evaluate the association between iron deficiency anemia and its severity with CPR during the third trimester of pregnancy.

## Methods

This was a prospective study approved by the Marmara University Faculty of Medicine (decision no: 09.2020.1144/ date: 06.11.2020), and conducted at Marmara University, in accordance with the Declaration of Helsinki. An informed consent form was obtained from the participants.

### Study Population and Inclusion Criteria

This study was planned as a prospective study to evaluate uncomplicated healthy singleton pregnant women who were admitted to Marmara University, Gynecology and Obstetrics Outpatient Department between 01/12/2020-01/12/2021 and had iron deficiency anemia after 28 weeks of gestation.

The inclusion criterion was pregnant women who delivered singletons between $28^{0/7}$ and $37^{0/7}$ weeks of gestation. The gestation week was determined by the last menstrual period. If the last menstrual period was unknown, the gestational week was determined using ultrasonographic measurements performed in the first trimester. The exclusion criteria were: (1) having multiple pregnancies, (2) preterm delivery prior to 37 weeks of gestation, (3) fetal chromosomal or congenital anomalies, (4) maternal use of tobacco, alcohol, or drugs, (5) Hb <4 mg/dL, and (6) presence of complications such as diabetes (pregestational or gestational), chronic hypertension, gestational hypertension, preeclampsia), preterm premature rupture of membrane, placenta previa, and placental abruption. In addition, pregnant women with thalassemia, sideroblastic anemia or megaloblastic anemia were also excluded from this study. The 108 pregnant women were divided into three groups according to anemia levels based on the WHO cutoffs (12): Hb 7-9.9 mg/dL (n=40), Hb 10-10.9 mg/dL (n=34), and Hb >11 mg/dL (n=34, control group). Iron deficiency anemia was defined when the serum ferritin level was less than 15 mcg/L and there was no infection (11). Anemia was classified as no anemia (Hb >11 mg/dL), mild anemia (Hb 10-10.9 g/dL), and moderate anemia (Hb 7-9.9 g/dL) based on the WHO cutoffs (12).

### Ultrasonographic Evaluations

The CPR was measured as previously described (13) by an experienced ultrasonographer. A Mindray DC-7 Ultrasound (Shenzhen Mindray Bio-Medical Electronics Co., Ltd, China) with a 3.5-MHz curvilinear transducer to perform the Doppler measurements. Doppler measurements for the UA was performed in the umbilical cord-free loops. The MCA was measured using a transverse Doppler image of the fetal head taken at the level of the sphenoid bone. The Circle of Willis was visualized using color flow Doppler and measured approximately 1 cm distal to the branching point from the internal carotid artery, with the insonation angle as close to 0 degrees as possible. The PI and resistivity index (RI) for each artery was calculated from the mean of three measurements taken during fetal apnea periods. The CPR was calculated from the MCA PI to UA PI ratio.

**Statistical Analysis**

Values were analyzed using the SPSS 22.0 package program. Mean, standard deviation, minimum, and maximum values were used for the descriptive variables. The ANOVA test was used to evaluate the difference between groups. The Spearmen correlation test was also used to evaluate the relationship between Hb level and cerebroplacental ratio. p<0.05 was considered statistically significant.

## Results

A total of 108 pregnant women, including 40 with moderate anemia, 34 with mild anemia, and 34 that were healthy, were included in the study. The mean Hb value of the pregnant women in the moderate anemia group was 9.1 mg/dL, in the mild anemia group was 10.4 mg/dL, and in the control group was 11.9 mg/dL. Demographic data of the pregnant women included in the study are given in Table 1. Age, gestational week, body mass index, gravidity, parity, abortion, and the number of surviving pregnant women were similar between the groups (p=0.747, p=0.112, p=0.054, p=0.609, p=0.416, p=0.854, and p=0.510, respectively).

The MCA PI was 1.89±0.34 in moderate anemia group, 1.63±0.32 in mild anemia group, and 1.57±0.39 in the control group (p<0.001). MCA RI values were similar between the groups (p=0.836). UA PI values were 0.92±0.18 in the moderate anemia group, 1.01±0.15 in the mild anemia group, and 1.01±0.14 in the control group (p=0.013). There was a significant difference between the groups in terms of UA RI values with 0.60±0.11 in the moderate anemia group, 0.64±0.09 in the mild anemia group, and 0.65±0.07 in the control group (p=0.042).

The CPR PI values were 2.11±0.43 in the moderate anemia group, 1.62±0.22 in the mild anemia group, and 1.56±0.4 in the control group (p<0.001). There was a difference between the groups and CPR PI value and a significant negative correlation was observed (r=-0.472, p<0.001) (Table 2).

## Discussion

In the third trimester of pregnancy, iron deficiency anemia is frequently seen due to rapid growth. Preventing iron deficiency in pregnancy is imperative to limiting iron deficiency in the fetus and the associated complications (14). This study aimed to evaluate the effect of iron deficiency anemia on CPR in the third trimester, which is used as a fetal development marker.

In this study, no difference was observed between the groups in terms of demographic characteristics. However, a decrease in Hb level resulted in (1) an increase in MCA PI and CPR PI values, and (2) a decrease in UA PI and UA RI values. Complications during pregnancy can cause acute and chronic hypoxia in the fetus. Acute hypoxia occurs during cord compression or labor, while chronic hypoxia occurs in conditions such as high altitude

**Table 1.** Comparison of anemia groups and demographic characteristics

| | Hemoglobin (mg/dL) | | | p |
|---|---|---|---|---|
| | 7-9.9 | 10-10.9 | >11 | |
| **Patients** | 40 | 34 | 34 | |
| **Age (year)** | 28.60±4.84 | 28.71±6.88 | 29.65±7.22 | 0.747 |
| **Gestational age (week)** | 32.7 (29-36) | 32.70 (28-36) | 33.35 (30-36) | 0.179 |
| **BMI (kg/cm²)** | 28.03±3.65 | 28.03±4.38 | 30.32±3.96 | 0.054 |
| **Gravida** | 2.47 (1-6) | 2.5 (1-6) | 2.81 (1-7) | 0.609 |
| **Parity** | 1.05 (0-3) | 1.13 (0-5) | 1.44 (0-6) | 0.416 |
| **Abortions** | 0.47 (0-4) | 0.38 (0-3) | 0.38 (0-2) | 0.854 |
| **Living** | 1.05 (0-3) | 1.13 (0-5) | 1.38 (0-5) | 0.510 |

Values were written as mean ± standard deviation or mean (maximum-minimum).
BMI: Body mass index

**Table 2.** Comparison and correlation of anemia groups and ultrasound parameters

| | Hemoglobin (mg/dL) | | | | Correlation | |
|---|---|---|---|---|---|---|
| | 7-9.9 | 10-10.9 | >11 | p | r | p |
| **MCA PI** | 1.89±0.34 | 1.63±0.32 | 1.57±0.39 | **0.000** | -0.285** | **0.003** |
| **MCA RI** | 0.72±0.12 | 0.73±0.09 | 0.73±0.11 | 0.836 | 0.081 | 0.403 |
| **UA PI** | 0.92±0.18 | 1.01±0.15 | 1.01±0.14 | **0.013** | 0.267** | **0.005** |
| **UA RI** | 0.60±0.11 | 0.64±0.09 | 0.65±0.07 | **0.042** | 0.279** | **0.003** |
| **CPR PI** | 2.11±0.43 | 1.62±0.22 | 1.56±0.4 | **0.000** | -0.472** | **0.000** |
| **CPR RI** | 1.24±0.26 | 1.16±0.19 | 1.14±0.18 | 0.103 | -0.215* | 0.026 |

Values were written as mean ± standard deviation
MCA: Middle cerebral artery, PI: Pulsatility index, RI: Resistance index, UA: Umbilical artery, CPR: Cerebroplacental ratio

living, anemia, smoking, maternal respiratory diseases, anemia, and preeclampsia (15). The resistance in the fetal cerebral artery is high in the prenatal period. However, this may change in placental insufficiency and hypoxemia in response to chemoreceptor stimulation or changes in vasodilators or vasoconstrictors (16). There are studies in the literature evaluating maternal iron deficiency anemia and fetal cerebral blood flow. Abdel-meged et al. (7) evaluated the effect of iron deficiency treatment on CPR and found that the mean MCA PI at admission was 1.42 in the control group, 1.41 in mild anemia group, 1.42 in moderate anemia group, and 1.56 in severe anemia group. MCA RI values were 0.821 in the control group, 0.734 in the mild anemia group, 0.81 in the moderate anemia group, and 0.70 in the severe anemia group. In addition, they found that there was an increase in CPR RI and UA RI values with anemia.

In the study conducted by Ali et al. (17) in which they evaluated fetal vascular adaptation before and after treatment in severe anemia, they concluded that the fetuses of individuals with severe maternal anemia showed altered MCA and UA flows, and they showed that vascular adaptation returned to normal after maternal anemia was treated. In their study, the UA PI and UA RI values were higher and the MCA PI and MCA RI values were lower in the anemia group. They showed that CPR RI rates were also lower in the anemia group. They found that after the treatment, MCA RI, MCA PI, UA PI, and UA RI values decreased due to adaptation and CPR RI rates increased. This has been interpreted as the fetus is adapting to anemic conditions by redistributing blood flow to the brain (17). In a study by Abdelsamie et al., (18) the MCA PI value was measured as 1.62±0.15 in the severe anemia group, 1.47±0.16 in the moderate anemia group, and 1.41±0.22 in the mild anemia group. These values showed that there was an increase in the PI value with anemia. The UA RI, UA PI, and MCA RI values also increased with anemia (18). In the current study, MCA PI values were 1.57±0.39 in the control group, 1.63±0.32 in mild anemia group, and 1.89±0.34 in moderate anemia group. The MCA PI and CPR PI values increased with the decrease in the Hb level and there was a decrease in the UA PI and UA RI values. In addition, although the MCA RI values were lower in the anemia group, no significant difference could be found between the groups.

It is well documented that the CPR RI rate decreases in the presence of hypoxia due to increased placental resistance and cerebral vasodilation (19). It may cause cerebral vasodilation due to hypoxia affecting the fetus during maternal anemia. Maternal anemia is a factor that affects the development of the fetus by creating a chronic hypoxic state in the fetus. In the case of anemia, the decrease in cerebral resistance has a protective effect on the brain by redistributing the blood flow to the brain. It stands out as a mechanism to protect the fetus from a hypoxic state by providing more blood flow from the placenta in response to a decrease of resistance in the uterine artery. Maternal anemia in pregnancy is a condition that should constantly be followed up. It can be evaluated biochemically as well as ultrasonographically. Redistribution and changes in UA and MCA are known in anemia. Fetal well-being in anemia in uncomplicated pregnancies can be evaluated with these values. If these parameters, which can be observed during routine follow-up, change, it should be kept in mind that maternal anemia may also be present in addition to FGR.

### Study Limitations

Since smoking is a confidential process in society, some of our patients hide their smoking during pregnancy or report it as less than it is. Although uncomplicated pregnancies were included, smoking and altitude that would cause chronic hypoxia were not questioned. In addition, although patients were selected in the last trimester, they were not all in the same week. The effect of severe acute respiratory syndrome coronavirus-2 on Doppler imaging was unknown and patients were not questioned whether they had an infection. The patients were evaluated only during the third-trimester follow-up in the clinic, and the effects of anemia and USG results on pregnancy outcomes were not evaluated. While selecting the groups, iron use during follow-up in the clinic was ignored because we did not observe the efficacy of the treatment.

## Conclusion

Maternal anemia is one of the chronic hypoxic conditions affecting the development of the fetus. It induces a vascular response as a fetal adaptation, which is shown by changes in UA and MCA. Our results suggested that MCA PI, UA PI, UA RI, and MCA/UA PI were altered in the presence of iron deficiency anemia in the third trimester of pregnancy.

### Ethics

**Ethics Committee Approval:** This was a prospective study approved by the Marmara University Faculty of Medicine (decision no: 09.2020.1144/date: 06.11.2020), and conducted at Marmara University, in accordance with the Declaration of Helsinki.

**Informed Consent:** An informed consent form was obtained from the participants.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.M.K., M.Ç., O.S.S., D.Ü., Concept: M.M.K., M.E.Ş., Design: M.M.K., Data Collection or Processing: M.M.K., M.Ç., O.S.S., D.Ü., Analysis or Interpretation: M.Ç., O.S.S., Literature Search: D.Ü., Writing: M.M.K., M.E.Ş.

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Original Article

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# Could the Umbilical Cord Suggest the Method of Anesthesia?

## Umblikal Kord Anestezi Yöntemini Gösterebilir Mi?

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## ABSTRACT

**Objective:** We aimed to investigate changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase-myocardial band (CK-MB), and troponin I levels, which were biochemical parameters that gave an idea regarding clinical conditions such as tissue damage and asphyxia, according to the anesthesia type, to compare their levels in mothers who gave birth with normal spontaneous vaginal delivery (NSVD) and to investigate whether the type of anesthesia applied caused a change in biochemical parameters.

**Methods:** Of the 90 patients included in the present study, 30 (33.3%) underwent general anesthesia, while 30 (33.3%) underwent spinal anesthesia, and 30 (33.3%) gave birth with NSVD. AST, ALT, LDH, CK-MB, and troponin I levels were measured in all pregnant women before they were taken to the operating room or delivery room. After the baby was delivered, a blood sample was taken from the umblical artery to measure AST, ALT, LDH, CK-MB, and troponin I levels. The APGAR scores, the need for oxygen, positive pressure ventilation, and intubation after delivery of the newborns were recorded.

**Results:** Statistically significant increases were found in AST, ALT, LDH, and troponin I levels in umblical artery in all groups when compared with their levels in pregnant women before delivery.

**Conclusion:** An increase in umbilical artery CK-MB and ALT levels was observed in the NSVD group. Due to the increase in umbilical artery CK-MB and ALT levels in the NSVD group, it was found that it was not appropriate to evaluate the effects of anesthesia on the newborn with these markers.

**Keywords:** Umbilical cord, lactate dehydrogenases, parturition, anesthesia

## ÖZ

**Amaç:** Doku hasarı, asfiksi gibi klinik durumlar hakkında fikir veren biyokimyasal parametreler olan aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), laktat dehidrogenaz (LDH), kreatin kinaz-miyokardiyal bant (CK-MB) ve troponin 1 değerlerinin anestezi tipine göre farklılığını araştırmayı amaçladık. Bu parametreleri genel anesteziyle, spinal anesteziyle ve normal spontan vajinal doğum (NSVD) doğum yapan gebelerde karşılaştırmayı ve uygulanan anestezi tipinin biyokimyasal parametrelerde değişikliğe neden olup olmadığını araştırmayı amaçladık.

**Yöntemler:** Çalışmaya dahil edilen 90 gebenin 30'una (%33,3) genel anestezi, 30'una (%33,3) spinal anestezi uygulandı ve 30'u (%33,3) NSVD ile bebek sahibi oldu. Tüm gebelerde ameliyathaneye veya doğuma alınmadan önce kan AST, ALT, LDH, CK-MB ve troponin 1 düzeyleri ölçüldü. Bebek doğduktan sonra umblikal arterden kan numunesi alındı ve AST, ALT, LDH, CK-MB ve troponin 1 düzeyleri ölçüldü. Yenidoğanların doğumundan sonra APGAR skorları, oksijen ihtiyacı, pozitif basınçlı ventilasyon ve entübasyon ihtiyacı not edildi.

**Bulgular:** Tüm gruplarda gebelerin doğumdan önceki kan değerleriyle karşılaştırıldığında umblikal arter AST, ALT, LDH ve troponin 1 düzeylerinde istatistiksel olarak anlamlı artışlar tespit edildi.

**Sonuç:** Normal spontan vajinal doğum grubunda umbilikal arter CK-MB ve ALT düzeylerinde artış gözlendi. NSVD grubunda umblikal arter CK-MB ve ALT düzeylerindeki artış nedeniyle anestezinin yenidoğan üzerindeki etkilerini bu belirteçlerle değerlendirmenin doğru olmadığı görüldü.

**Anahtar Sözcükler:** Umblikal kord, laktat dehidrogenaz, doğum, anestezi

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## Introduction

The rate of cesarean section has increased gradually worldwide and in our country in the last twenty years (1-4). In the Turkish Statistical Institute, Child with Statistics, 2020 bulletin, it was revealed that while the rate of cesarean deliveries in live births was 51.1% in 2014, it was 54.4% in 2019 (4).

The increase in the number of cesarean sections and the impacts of spinal and general anesthesia on the mother and fetus have been compared and investigated in many studies. General and spinal anesthesia techniques used in cesarean sectionare known to have pros and cons peculiar to them. Advantages of general anesthesia include rapid induction, less hypotension, decreased cardiovascular depression, good airway, and respiratory control. Prominent advantages of regional anesthesia, which has been preferred more frequently in recent years, are that the patient is conscious, the risk of aspiration is minimal, and it does not lead to respiratory depression in the newborn.

Although first, fifth, and tenth-minute APGAR scores are the most commonly used method in the evaluation of the clinical condition of the neonate, it has been suggested that umbilical cord blood gases are more reliable as they are not correlated with temporary intrapartum and late neurological injuries and are impacted by various factors (4,5). Although pH has been reported to be the parameter that best indicates fetal status from umbilical cord artery blood gas values, studies have revealed that lactate concentration is more valuable, especially regarding fetal distress (5).

In our study, we investigated the changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase myocardial band (CK-MB), and troponin I levels according to the anesthesia method. We evaluated the change in the levels of the same blood parameters of the fetus with anesthesia method, APGAR score, placental separation time, age and gestational week.

## Methods

Pregnant women who gave birth with the diagnosis of term pregnancy between January 2021 and December 2021 were prospectively included in the present study. This study was conducted in accordance with the Declaration of Helsinki. After obtaining the ethics committee approval, this study was started prospectively (number: E-37201737-806.02.02) on 60 healthy pregnant women who were expecting a single baby, were between the ages of 18-40, had the American Society of Anesthesiologists score II, and were between 35-41 weeks of gestation, with an indication for elective cesarean section in gynecology and obstetrics clinic and on 30 pregnant women who were planned for normal spontaneous vaginal delivery (NSVD). Pregnant women were informed about this study, and their written and verbal consents were obtained. Patients who underwent emergency cesarean section or NSVD, pregnant women with HELLP, preeclampsia, eclampsia, liver disease, renal disease, cardiovascular disease or any other pregnancy-related disorder, pregnant women with multiple pregnancies, and pregnant women with abnormally high biochemical parameters in blood samples were excluded from the study. Pregnant women with Rh incompatibility, expected fetal anomaly, risk of meconium aspiration, or placental location or adhesion anomaly were excluded from this study.

The AST1, ALT1, LDH1, CK-MB1 and troponin II levels were measured in all pregnant women before they were taken to the operating room or delivery room. Vascular access was established with a 20 G angiocath from the back of the hand or antecubital region in all pregnant women, and crystalloid fluid (0.9% NaCl) infusion was started. The pregnant women included in the present study were divided into three groups: Group G (Group under general anesthesia, n=30), Group S (Group with spinal anesthesia, n=30), and Group V (Group with NSVD n=30). Group randomization was performed according to the preferences of the pregnant women and the evaluation of the obstetrician and gynecologist. Electrocardiography, heart rate, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, and peripheral oxygen saturation ($SpO_2$) were monitored in all groups following they were placed on the operating table. In Group G, anesthesia was induced with 2 mg/kg propofol and 0.6 mg/kg rocuronium. After muscle relaxation was achieved, the pregnant women were intubated. Patients were provided with volume-controlled ventilation to achieve a tidal volume of 6-8 mL/kg, respiratory frequency of 10-12/min, PEEP: 4 cm $H_2O$, and I:E 1/2. 50% oxygen-50% air mixture and 1 minimum alveolar concentration. Sevoflurane was administered for maintenance of anesthesia. When necessary, 0.15 mg/kg rocuronium was added. After the baby was delivered and the umbilical cord was clamped, 1 mcg/kg fentanyl was administered intravenously to the pregnant women as an analgesic.

In the Group S, the pregnant women were placed in a sitting position and the puncture site was wiped with povidone-iodine poly iodine complex and covered with a perforated sterile drape. After sterile conditions were achieved, the subarachnoid space was entered slowly with a 25 G (25 G Quincke) spinal needle from the midline of the L3-4 or L4-5 vertebral space in the intervention area. After the clear cerebrospinal fluid was seen to come, 2.0-2.4 mL (10-12 mg) of 0.5% hyperbaric bupivacaine (Busacain Spinal Heavy 4 ml-Haver, Istanbul, Turkey) was slowly administered into the subarachnoid space. The operation was allowed upon the sensory and motor block were at an adequate level.

After the baby was delivered and the umbilical cord was clamped, a sterile sample was taken from the umbilical artery by the same Gynecologist. AST2, ALT2, LDH2, CK-MB2, and Troponin I2 levels were measured in the blood samples taken.

The newborns were evaluated by a pediatrician. The APGAR score at the 1$^{st}$ and 5$^{th}$ minutes, the need for oxygen, positive pressure ventilation, and intubation after delivery of the newborns were recorded.

In Group V, the umbilical cord was clamped by midwives, and blood samples were taken from the umbilical artery immediately after the birth of the fetus in the delivery room.

**Statistical Analysis**

The software of SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics were expressed as numbers and percentages for categorical variables, while they were expressed as mean, standard deviation, minimum, maximum, median, and interquartile range for numerical variables. Comparisons of numerical variables in more than two independent groups were made with the one-way ANOVA test when the normal distribution condition was met in the groups and with the Kruskal-Wallis test when the condition was not met. Subgroup analyses were conducted via the Mann-Whitney U test and interpreted with Bonferroni Correction. Correlations between numerical variables were determined by Spearman Correlation Analysis since the parametric test condition was not met. Statistical alpha significance level was considered to be $p<0.05$.

## Results

Of the 90 patients included in the present study, 30 (33.3%) underwent general anesthesia, while 30 (33.3%) underwent spinal anesthesia, and 30 (33.3%) had NSVD. The mean age of the Group V was significantly lower than the Group G and Group S (general vs. NSVD p=0.042 spinal vs. NSVD p=0.021). The removal duration of placenta in the Group G was significantly longer than the Group S (p<0.001). A significant difference was found between the APGAR scores of the groups (p=0.023). The APGAR score of the Group G was significantly lower than the Group V (p=0.007).

A significant difference was determined between the AST1 and AST2 levels of the all groups (p=0.042). In all groups, the sample taken from the mother before the birth and the sample taken from the umbilical cord after the birth were evaluated and the increase in the AST level was found to be significant (p=0.001, p=0.039 and p<0.001). The AST level of the Group G was higher than the Group S (p=0.016). A significant decrease was found in the ALT level of the Group S, whereas a significant increase was found in the Group V (p=0.001 and p=0.016). It was found that there was a significant difference in the ALT2 level, difference, and % change of the all groups (p=0.001, p=0.001 and p<0.001, respectively) (Table 1).

No significant difference was determined between the groups regarding troponin 1 levels (p=0.780). The increase in troponin levels was significant for all groups (p=0001, p<0.001 and p=0.010, respectively). A significant difference was found in the troponin II level, difference, and % change of the all groups (p<0.001 for all). troponin II, difference, and % change levels were significantly higher in the Group S than the Group G and V (p<0.001 for all) (Table 1).

A significant difference was found in LDH 1 levels of the groups (p=0.007). LDH 1 level was higher in the Group V than the Group S (p=0.002). The increase in LDH levels of all groups was statistically significant (p<0.001 for all) (Table 2). Similarly, in our study, a significant difference was found between the groups' umbilical artery LDH values (LDH 2) and maternal LDH levels (LDH 1) (p<0.001 and p=0.038, respectively). The difference between maternal and umbilical artery LDH levels in the Group G was significantly higher than in the Group S (p<0.001, p=0.001 and p=0.013) (Tables 1, 2).

No significant difference was found between the groups concerning CK-MB1 levels (p=0.053). Difference and % change were higher in the Group V than Group G and Group S,. whileCK-MB2 level was higher in the Group V compared to the Group G (p<0.001, p=0.004, p=0.006 and p=0.012, respectively). A significant difference was found between the groups regarding the CK-MB2 level, difference, and % change (p=0.001, p=0.012 and p=0.033, respectively) (Table 1).

A significant positive correlation was found between duration of placental removal and LDH2 level in all groups (p=0.020). In our study, a significant positive correlation was found between duration of placental removal and LDH2 level in all groups (p=0.012 and p=0.020, respectively), while the duration of placental removal in the Group G was significantly longer than in the Group S (p<0.001) (Table 3).

None of the neonates needed intubation or respiratory support. None of the pregnant women needed respiratory support and intensive care after delivery.

## Discussion

The superiority of general and spinal anesthesia administered in pregnant patients during cesarean delivery, which has become one of the most frequently performed surgical procedures today, to each other could not be shown in studies (6-8). With the increase in the number of cesarean sections performed, how the newborn is impacted by anesthesia has been investigated. Although there are many studies on this issue, the effects of anesthesia type on the newborn still attracts attention. In the evaluation of the newborn, the blood sample taken from the umbilical cord has been studied with a great variety of parameters (9-11). It has been revealed that umbilical artery blood gas values are guiding in determining hypoxemic and acidic newborns (9,10).

There are many studies investigating the effects of umbilical cord blood gas values and anesthesia on the newborn and the effects of bupivacaine on the umbilical artery (5,11,12). Maternal hypotension caused by regional anesthesia may affect uteroplacental blood flow, resulting in fetal acidosis, asphyxia, and low Apgar scores (12,13). By measuring umbilical artery LDH levels, it is supported that LDH is a sensitive marker in showing stress in the intrapartum period (14). It has also been demonstrated that it can be a marker of hypoxic-ischemic encephalopathy (HIE) in the first 12 hours after birth, and the relationship between severity of HIE and LDH levels in newborns is promising (15-17). Reddy et al. (18) reported in their study that LDH was the most accurate test in the first 72 hours to distinguish asphyxia in newborns. Likewise, in our study, LDH2 level was found to be significantly increased compared to LDH1 in all groups. However, since LDH level is affected by various factors and its level increases with hemolysis, its use in evaluating the effects of anesthesia on the newborn is limited.

Crawford et al. (14) have suggested that the most significant factor that can affect the oxygenation and acid-base status of the fetus at birth is the duration between uterine incision and delivery. In our study, a significant positive correlation was found between duration of placental removal and LDH2 level in all groups. The duration of placenta removal of the Group G was significantly longer than the Group S. We are of the opinion that the reason for the higher elevation in LDH2 level in the Group G is due to the length of duration for placental removal in pregnants undergoing the cesarean section under general anesthesia.

Although AST and ALT may increase due to many reasons in the fetus, they may also increase idiopathically (19). In our study, it was observed that ALT2 level decreased compared to ALT1 level in Group S, while an increase was found in Group V, which did not receive anesthesia. Therefore, we think that spinal anesthesia may not have a direct effect on the change in ALT levels.

The CK-MB and troponin I levels can be affected by various pathological conditions, such as HIE and asphyxia (20,21). Wan et al. (20) reported that there was a significant correlation between

**Table 1.** Change according to anesthesia method

| | Group G | Group S | Group V | p* |
|---|---|---|---|---|
| AST1 | 25.3±8.4 | 20.7±7.1 | 22.2±6.8 | 0.042 |
| AST2 | 38.6±18.7 | 29.8±17.8 | 33.1±11.4 | 0.063 |
| Difference | 12 (0-21.5) | 3 (-5-18.25) | 8 (3-18) | 0.256 |
| P | 0.001* | 0.039* | <0.001* | |
| % change | 48.7 (0.0-146.3) | 11.7 (-19.7-111.5) | 40.4 (14.3-107.3) | 0.426 |
| ALT1 | 15.4±7.7 | 14.0±6.5 | 11.4±5.5 | 0.039 |
| ALT2 | 16.3±8.4 | 10.0±5.1 | 14.8±6.2 | 0.001 |
| Difference | 1.5 (-5-6.5) | -3.5 (-5.75- -0.75) | 2.5 (-1-7) | 0.001 |
| P | 0.459* | 0.001* | 0.016* | |
| % change | 13 (-31.3-52) | -25.6 (-45.8- -6.3) | 22.6 (-9.1-90.6) | <0.001* |
| TROP1 | 0.0035±0.0016 | 0.0064±0.0133 | 0.0038±0.0041 | 0.780 |
| TROP2 | 0.0051±0.0021 | 0.0384±0.1112 | 0.0044±0.0021 | <0.001* |
| Difference | 0.0011 (-0.00015-0.0035) | 0.0049 (0.0027-0.0088) | 0.0007 (0-0.0024) | <0.001* |
| P | 0.001* | <0.001* | 0.010* | |
| % change | 33.1 (-3.6-140.9) | 203.6 (93.6-634) | 26.5 (0.0-93.4) | <0.001* |
| LDH1 | 290.6±82.5 | 247.1±64.8 | 307.1±78.5 | 0.007 |
| LDH2 | 495.1±147.1 | 387.3±197.8 | 475.8±126.9 | <0.001* |
| Difference | 179.5 (100-313.5) | 111 (64.75-144.75) | 165 (93.75-251) | 0.038 |
| P | <0.001# | <0.001# | <0.001* | |
| % change | 68.1 (34.2-123.2) | 47.4 (25.7-77.6) | 52.8 (29.0-88.1) | 0.384 |
| CK-MB1 | 1.90±0.99 | 1.73±1.01 | 2.33±1.06 | 0.053 |
| CK-MB2 | 1.97±2.14 | 2.17±2.20 | 3.87±2.78 | 0.001 |
| Difference | 0 (-1-0.25) | 0 (-1-1) | 1 (0-3.25) | 0.012 |
| P | 0.484# | 0.612# | 0.002# | |
| % change | 0.0 (-50-25) | 0.0 (-33.3-100) | 66.7 (0.0-100) | 0.033 |

*P-value <0.05 is considered as statistically significant difference
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CK-MB: Creatine kinase myocardial band

**Table 2.** The amount of change according to anesthesia method

| | AST difference | ALT difference | TROP difference | LDH difference | CK-MB difference |
|---|---|---|---|---|---|
| | p | p | p | p | p |
| Group G vs Group S | 0.156* | 0.0167* | <0.001* | 0.013* | 0.393 |
| Group G vs Group V | 0.668 | 0.446 | 0.515 | 0.451 | 0.006* |
| Group S vs. Group V | 0.167* | <0.001* | <0.001* | 0.082 | 0.028 |
| | AST change | ALT change | TROP change | LDHD change | CK-MB change |
| Group G vs Group S | 0.304 | 0.013* | <0.001* | 0.174 | 0.273 |
| Group G vs Group V | 0.882 | 0.222 | 0.535 | 0.379 | 0.012* |
| Group G vs Group V | 0.220 | <0.001* | <0.001* | 0.631 | 0.103 |

Mann-Whitney U test Bonferroni correction p<0.017
*P-value <0.05 is considered as statistically significant difference.
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CK-MB: Creatine kinase-myocardial band

**Table 3.** Clinical features

| | Age | | Gestational week | | Duration of placenta removal | | APGAR | |
|---|---|---|---|---|---|---|---|---|
| | r | p | R | p | r | p | R | p |
| AST1 | 0.094 | 0.381 | 0.115 | 0.282 | 0.162 | 0.215 | -0.002 | 0.984 |
| AST2 | -0.011 | 0.917 | 0.015 | 0.888 | 0.233 | 0.074 | -0.024 | 0.823 |
| AST difference | -0.065 | 0.542 | -0.077 | 0.473 | 0.125 | 0.341 | 0.000 | 0.996 |
| AST change | -0.085 | 0.424 | -0.069 | 0.518 | 0.104 | 0.428 | 0.017 | 0.877 |
| ALT1 | 0.167 | 0.116 | 0.051 | 0.632 | 0.217 | 0.096 | -0.157 | 0.140 |
| ALT2 | -0.098 | 0.360 | 0.097 | 0.361 | 0.224 | 0.085 | -0.188 | 0.076 |
| ALT difference | -0.123 | 0.246 | 0.012 | 0.912 | 0.035 | 0.789 | -0.027 | 0.803 |
| ALT change | -0.164 | 0.123 | 0.004 | 0.970 | 0.061 | 0.646 | -0.048 | 0.652 |
| TROP1 | 0.212 | 0.045* | 0.004 | 0.970 | 0.322 | 0.012* | 0.079 | 0.458 |
| TROP2 | 0.195 | 0.066 | -0.055 | 0.607 | -0.230 | 0.077 | 0.043 | 0.689 |
| TROP difference | 0.020 | 0.851 | -0.032 | 0.763 | -0.299 | 0.020* | 0.072 | 0.503 |
| TROP change | 0.012 | 0.914 | 0.000 | 0.999 | -0.321 | 0.012* | 0.065 | 0.545 |
| LDH1 | 0.142 | 0181 | 0.087 | 0.413 | 0.097 | 0.460 | -0.194 | 0.067 |
| LDH2 | -0.092 | 0.386 | 0.001 | 0.994 | 0.261 | 0.044* | -0.010 | 0.928 |
| LDH difference | -0.164 | 0.122 | -0.040 | 0.705 | 0.198 | 0.129 | 0.100 | 0.348 |
| LDH change | -0.196 | 0.064 | -0.034 | 0.749 | 0.140 | 0.285 | 0.181 | 0.087 |
| CK-MB1 | -0.065 | 0.541 | -0.025 | 0.812 | -0.010 | 0.938 | 0.120 | 0.262 |
| CK-MB2 | -0.143 | 0.179 | -0.218 | 0.039* | 0.063 | 0.630 | 0.131 | 0.219 |
| CK-MB change | -0.095 | 0.373 | -0.205 | 0.053 | 0.063 | 0.634 | 0.054 | 0.614 |
| CK-MB difference | -0.093 | 0.383 | -0.196 | 0.065 | 0.073 | 0.580 | 0.079 | 0.462 |

*P-value <0.05 is considered as a statistically significant difference.
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CK-MB: Creatine kinase-myocardial band

umbilical cord CK-MB and troponin I levels and neonatal HIE (NHIE). In addition, Sanjay et al. (21) revealed that CK-MB in the first eight hours and LDH levels in the first 72 hours in newborns could help to distinguish between asphyxiated and non-asphyxiated newborns.

In our study, however, no pathological levels were found in the effects of anesthesia and operation/delivery on the fetus with CK-MB and troponin I evaluation. The change in CK-MB2 levels was higher in the Group V than the Group G. However, as in other biochemical markers we studied, CK-MB and troponin I levels were impacted by many pathological conditions, such as HIE and asphyxia. Moreover, we think that it is not appropriate to use anesthesia alone to assess the effects of anesthesia on the neonate since there is a higher increase in the Group V than in the Group G.

**Study Limitations**

Since the mean duration to placenta removal was 7.37±0.49 minutes even in the general anesthesia group, the inability to analyze whether this duration was adequate to make an assessment with biochemical parameters constituted the limitations of our study, in which we tried to evaluate the effects of anesthesia on the neonate. Another limitation of the study was the fact that our study was conducted in a single center and with a small sample size.

## Conclusion

In our study, it was observed that ALT2 level was decreased compared to ALT1 in Group S, while an increase was found in Group V, which did not receive anesthesia. Therefore, we think that spinal anesthesia may not have a direct effect on the change in ALT levels.

Due to the increase in CK-MB2 and ALT2 levels in the Group V, it was found that it was not appropriate to evaluate the effects of anesthesia on the newborn with these markers. We need more specific markers to evaluate the effects of anesthesia on the fetus at an early time.

**Ethics**

**Ethics Committee Approval:** After obtaining the ethics committee approval, this study was started prospectively (number: E-37201737-806.02.02).

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

**Peer-review:** Externally peer reviewed.

**Authorship Contributions**

Surgical and Medical Practices: E.Ç., Ö.T., Concept: E.Ç., Ö.T., Design: E.Ç., Data Collection or Processing: E.Ç., Ö.T., Analysis or Interpretation: Ö.T., Literature Search: E.Ç., Ö.T., Writing: E.Ç.

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Original Article

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# Psychological Outcomes 1 Year After Restrictive Bariatric Surgery

## Kısıtlayıcı Bariatrik Cerrahiden 1 Yıl Sonraki Psikolojik Sonuçlar

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### ABSTRACT

**Objective:** To reveal the depression and body image changes observed in patients undergoing bariatric surgery.

**Methods:** This prospective study followed a descriptive-correlational study design. The study population consisted of patients hospitalized in the general surgery clinic of a university hospital in order to evaluate the depression symptom level and body image of patients undergoing bariatric surgery. The study sample comprised 22 patients who were admitted to the general surgery clinic of the same hospital and met the following criteria: being over 18 years of age, being fully oriented (time, person, place) and conscious, being able to see, hear, being able to read, write, speak and understand Turkish, being diagnosed as having obesity, being hospitalized for sleeve gastrectomy, and willing to participate in the study. The data for the study were collected using a Personal Information Form prepared by the investigators, the body cathexis scale (BCS) and the beck depression inventory (BDI)

**Results:** Twenty two patients, 16 of whom were female, with a mean age of 31.18±7.79 years were included. The body mass index (BMI) (kg/m$^2$) values recorded 1 year after the operation were significantly lower than the baseline levels (Z=-4.107; p=0.000). The mean BCS score 1 year after the operation was significantly lower than at the time of the baseline evaluation (t=3.447; p=0.002). The baseline BMI (kg/m$^2$) value and BDI score were found to be positively correlated (r=0.448; p=0.036). The baseline BDI score increased

### ÖZ

**Amaç:** Bu çalışmanın amacı bariatrik cerrahi geçiren hastalarda gözlenen depresyon ve beden algısı değişimlerini ortaya koymaktır.

**Yöntemler:** Prospektif çalışma tanımlayıcı ve ilişki arayıcı niteliktedir. Bariatrik cerrahi geçiren hastaların depresyon belirti düzeyi ve beden algısının sürece bağlı değerlendirilmesi amacıyla bir üniversite hastanesinin genel cerrahi kliniğinde yatan hastalar çalışma evrenini oluşturmuştur. Örneklemi ise aynı hastanenin genel cerrahi kliniğinde; 18 yaşından büyük, yönelimi tam (zaman, kişi, yer) ve bilinci açık, görebilen, işitebilen, Türkçeyi okuma, yazma, konuşabilme ve anlayabilme becerisine sahip, obezite tanısı konmuş, ameliyat olmak üzere hastaneye yatırılmış ve araştırmaya katılmayı kabul eden 22 hasta oluşturmuştur. Çalışma verileri Kişisel Bilgi Formu ile beden algısı ölçeği (BAÖ) ve beck depresyon ölçeği (BDÖ) kullanılarak toplanmıştır.

**Bulgular:** Çalışma yaş ortalaması 31,18±7,79 yıl olan 16'sı kadın 22 hasta üzerinde gerçekleştirildi. Ameliyattan bir yıl sonraki beden kütle indeksi (BKİ) (kg/m$^2$) değerleri, ilk değerlendirmeye göre anlamlı ölçüde daha düşüktür (Z=-4,107; p=0,000). Ameliyattan bir yıl sonraki BAÖ puan ortalamaları, ilk değerlendirmeye göre anlamlı ölçüde daha düşüktür (t=3,447; p=0,002). Ön test BKİ (kg/m$^2$) ile BDÖ skoru arasında pozitif yönde, zayıf derecede istatistiksel olarak anlamlı ilişki tespit edilmiştir (r=0,448; p=0,036). BKİ (kg/m$^2$) arttıkça ön test BDÖ puanları artmış aynı şekilde, BKİ (kg/m$^2$) azaldıkça, ön test BDÖ puanları azalmıştır.

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## ABSTRACT

with increased BMI (kg/m$^2$) value, and baseline BDI score decreased with decreased BMI (kg/m$^2$) value.

**Conclusion:** The patients were found to have lost a significant amount of body weight one year after the bariatric surgery. The baseline borderline clinical depression and an intermediate level of depression were found to change toa mild depression one year after bariatric surgery. Bariatric surgery was determined to have a positive effect on body image perception.


**Keywords:** Obesity, bariatric surgery, depression, perception of body image


## ÖZ

**Sonuç:** Hastaların bariatrik cerrahiden bir yıl sonra önemli bir kilo kaybı yaşadığı, ameliyat öncesi sınırda klinik depresyonun veya orta düzey depresyonun, bir yıl sonra hafif depresyon olarak değişim gösterdiği ve bariatrik cerrahinin beden algısını olumlu yönde etkilediği belirlendi.


**Anahtar Sözcükler:** Obezite, bariatrik cerrahi, depresyon, beden algısı

## Introduction

Obesity, which is defined as abnormal or excess fat storage in the body, is a complex, chronic and multifactorial disease that adversely affects health (1,2). The increase in obesity prevalence has caused the disease to become a worldwide public health problem (2-4). Obesity is the cause of chronic somatic comorbidities such as type 2 diabetes and metabolic syndrome, cardiovascular diseases, obstructive sleep apnea, osteoarthritis, gastroesophageal reflux disease, hepatobiliary diseases and polycystic ovary syndrome (5-7).

There are studies showing that bariatric surgery, which is applied in patients in whom there is no response to traditional methods such as diet, calorie restriction, exercise, or malabsorptive medical treatments, generally results in effective and permanent weight loss, resulting in improvement in somatic comorbidities and long-term survival (2,8-12). In the current literature, the indications of bariatric surgery are still controversial, and bariatric surgery is generally recommended for class 2 obese patients with somatic comorbidities and class 3-4 obese patients with or without comorbidity (13). In addition to restricting food intake, bariatric surgery is an effective treatment method in the recovery of obesity and related diseases caused by hormonal and neural changes (14).

Many bariatric surgery candidates are known to suffer from mental health disorders, particularly depression symptoms and binge eating disorder (15). Therefore, psychological evaluations and interventions before and after bariatric surgery, and a multidisciplinary approach to the treatment of obesity are important (16,17). A recent meta-analysis reports that the preoperative depression score is not predictive of postoperative weight change (18). However, it has been suggested that weight loss after bariatric surgery is associated with a short- and medium-term decrease in depression levels (19,20). According to long-term follow-up data, it has been reported that some patients did not receive psychological benefits after bariatric surgery, new depressive symptoms developed, or depressive symptoms that initially resolved after surgery returned back (12).

In the literature, a limited number of studies evaluating body image and depression symptoms in patients undergoing bariatric surgery have not reached the desired level (12,21-24). In the studies, it was determined that the changes specific to the society were not adequately examined. With this study, we aimed to analyze this. The aim of this study is to reveal the depression symptom level and body image changes observed in patients undergoing bariatric surgery.

## Methods

This prospective study was descriptive and correlational. The population of the study consisted of 31 patients hospitalized in the general surgery clinic of a university hospital between January 2015 and January 2016 in order to evaluate the depression and body image of patients undergoing bariatric surgery. In the study, it was aimed to reach the whole universe, which was not used for sampling. Inclusion criteria for the study were; being over 18 years of age, being fully oriented (time, person, place) and conscious, being able to see, hear, being able to read, write, speak and understand Turkish, being diagnosed as having obesity, being hospitalized for sleeve gastrectomy, and willing to participate in the study. Patients with a psychiatric diagnosis were excluded from the study. Twenty two patients in follow-up were reached again one year after surgery. Five patients who were diagnosed as having depression and received drug therapy were excluded from the study. Four patients did not participate in the study voluntarily. The general surgery clinic had a total of 37 beds and 46 patients underwent bariatric surgery in the same time period. Sleeve gastrectomy was performed in 31 patients and gastric bypass was performed in 15 patients. A total of 12 nurses worked in the clinic and three physicians were responsible for the same patient group. Patients were routinely evaluated by a psychiatrist before surgery.

### Ethical Approval

The study was conducted after obtaining ethics committee approval (date: 23.08.2013, number: 22 decision no: 15) from the Non-Invasive Clinical Research Ethics Committee of Çukurova University Faculty of Medicine and institutional permissions from the hospital where the research was conducted. The patients who accepted to participate in the study were given detailed information about the study and their written consent was obtained. In addition, the study was carried out in accordance with the principles of the Declaration of Helsinki 2008.

**Data Collection Tools**

The data of the study were collected using three different forms before bariatric surgery. These forms were the Personal Information Form prepared by the researchers, the Body Perception Questionnaire and the beck depression inventory (BDI). Personal Information Form, which was one of the pre-test data, was interviewed face-to-face with the patients by the researcher, and the other forms were filled in by the patients under the supervision of the researcher. Post-test data were collected at the 1st postoperative year during the outpatient follow-up.

**Personal Information Form**

The form prepared by the researchers was a literature-based questionnaire consisting of six questions in which descriptive characteristics were recorded (age, gender, marital status, educational status, family history of obesity, and body mass index (BMI) (20).

**Body Cathexis Scale**

The body cathexis scale (BCS) developed by Secord and Jourard aims to measure how satisfied individuals are with various body parts and body functions (25). The validity study of the questionnaire in Turkey was conducted by Hovardaoğlu and the Cronbach alpha reliability coefficient was determined as 0.91 (26). In this study, the Cronbach's alpha value was found to be 0.87. The Turkish version of the scale consists of 40 items, each of which is related to an organ or body part (such as arm, leg, face) or a function (such as sexual activity level). Each item is scored on a 5-point Likert-type scale ranging from 1 to 5 (1= I like it very much, 2= I like it a lot, 3= I am undecided, 4= I don't like it very much, 5= I don't like it at all). The most positive statement gets 1 point and the most negative statement gets 5 points. Accordingly, the lowest total score that can be obtained is 40, and the highest total score is 200. An increase in the total score obtained from the scale indicates a decrease in the person's satisfaction with his/her body parts or function, while a decrease in the score indicates an increase in satisfaction (26).

**Beck Depression Inventory**

Developed by Beck et al. (26), BDI was adapted into Turkish by Hisli (27). The Cronbach's alpha coefficient for BDI was 0.74 in the Turkish population. In this study, the Cronbach's alpha value was found to be 0.78. BDI is a 21-item, four-point scale used to evaluate depressive symptoms, ranging from seldom or never (0) to often or always (3), with a maximum score of 63 (1-10 normal, 11-16 mild depression, 17-20 borderline clinical depression, 21-30 moderate depression, 31-40 severe depression, and >40 major depression) (28).

**Statistical analysis**

Statistical analyzes were performed using the package program SPSS (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used during the interpretation of the findings. Kolmogorov-Smirnov normality test was applied to examine the distribution of the data. Parametric methods were used for measurement values suitable for normal distribution. "Independent Sample-t" test (Z-table value) was used when comparing the measurement values of two independent groups. The "Paired Sample" test (t-table value) was used when comparing the measurement values of two dependent groups, and the "Analysis of Variance" (F-table value) method was used when comparing the measurement values of three or more independent groups.

Non-parametric methods were applied to the measurement values that did not conform to the normal distribution. "Mann-Whitney U" test (Z-table value) was used when comparing the measured values of two independent groups. The "Wilcoxon" test (Z-table value) method was used when comparing the measurement values of the two dependent groups. Pearson correlation coefficient was used to analyze the relationships of two quantitative variables with normal distribution, and Spearman correlation coefficient was used in cases where at least one of them did not show normal distribution.

## Results

It was determined that the mean age of the participants was 31.18±7.79 years, 72.7% were women, 50% were married, 50% were at secondary education level and 72.7% had obese individuals in their families. It was determined that 72.7% of the patients were morbidly obese in the first preoperative evaluations, and 59.1% of them were obese in the first-year follow-ups (Table 1). The mean weight at baseline (Z1) was 131.6 kg (±23.6), 1 year later (Z2) was 92.0 kg (±19.4). It was determined that the participants lost an average of 69.9% of their initial weight 1 year after the surgery.

BMI ($kg/m^2$) values differed significantly according to the processes (Z=-4.107; p=0.000). One year post-operative BMI ($kg/m^2$) values were significantly lower than the initial evaluation. BCS score averages did not differ significantly according to the processes (p>0.05). BDI score averages differed significantly according to the processes (t=3.447; p=0.002). Satisfaction with body parts and body functions increased one year after surgery (Table 2).

The mean scores of BDI and BCS before and after surgery did not differ significantly according to the variables (p>0.05) (Table 3).

A positive, weak, statistically significant relationship was found between pre-test BMI ($kg/m^2$) and BDI (r=0.448; p=0.036). As BMI ($kg/m^2$) increased, pre-test BDI scores increased, and as BMI ($kg/m^2$) decreased, pre-test BDI scores decreased. There was no statistically significant correlation between post-test BDI scores and BMI ($kg/m^2$) (p>0.05). No statistically significant correlation was found between pretest-posttest BCS scores and BMI ($kg/m^2$) (p>0.05) (Table 4).

## Discussion

The results of the study revealing the differences between BMI, depression symptom level and body image levels in obese patients before and 1 year after bariatric surgery, and the relationship

between BMI before and 1 year after surgery and depression symptom level and body image levels were discussed in the light of the literature.

It was determined that patients experienced significant weight loss 1 year after bariatric surgery. In addition, the mean BMI scores one year after bariatric surgery differed significantly. BMI score averages were significantly lower in the second evaluation than in the first evaluation. These results were consistent with the findings of the study and meta-analysis (20,29,30). According to these results, it can be concluded that bariatric surgery used in the treatment of obesity has positive effects on weight loss and reducing BMI.

In the study, the mean BCS scores differed significantly one year after bariatric surgery. BCS score averages were significantly lower than the initial assessment. According to these findings, it can be concluded that bariatric surgery affects body image positively. In a study examining the effects of bariatric surgery on body image, it was found that there was a significant improvement in variables such as general body image, appearance evaluation, orientation and body satisfaction 3 months after surgery compared to preoperatively (31). Similar to the study in the literature, it was shown that body image changed positively after bariatric surgery (19,32-34,30). According to these findings; it can be concluded that bariatric surgery has a positive effect on body image.

It is not clear whether the negative body image observed in obese individuals is a result of obesity or a cause. Studies related to obesity show that there is a relationship between BMI and body image (35-37). This situation can be evaluated as the change in physical appearance with the decrease in BMI, as well as the positive effect on body image. However, an important issue to understand is that body image has a powerful effect on psychological health.

In the study, as preoperative BMI (kg/m$^2$) increased, pre-test BDI scores increased, and as BMI (kg/m$^2$) decreased, pre-test BDI scores decreased. Lifelong mental disorders are common in bariatric surgery candidates (38-40). It is known that obesity is associated with depression in particular (19,41,42). In addition, although the preoperative and one year post-operative BDI mean scores did not differ significantly, borderline clinical depression (27.3%) or moderate depression (18%) changed to mild depression one year later (72.6%). In this case, it can be concluded that the level of depression symptoms decreases with the weight loss experienced. However, unlike the change in weight and BMI, no significant difference was observed in terms of depression symptom levels. While this result is consistent with some studies in the literature (19,20), some studies show that existing depression persists and even increases after bariatric surgery (30,31,43,44). In addition, these findings suggest that depression may be another obesity comorbidity that can be

**Table 1.** Distribution of descriptive characteristics (n=22)

| Variables | n | % |
|---|---|---|
| **Age [$\bar{X}$ ± SD → 31.18±7.79 (years)]** | | |
| <30 | 10 | 45.5 |
| 30-40 | 7 | 31.8 |
| >40 | 5 | 22.7 |
| **Gender** | | |
| Male | 6 | 27.3 |
| Female | 16 | 72.7 |
| **Marital status** | | |
| Married | 11 | 50.0 |
| Single | 11 | 50.0 |
| **Education status** | | |
| Primary education | 5 | 22.7 |
| Secondary education | 11 | 50.0 |
| High education | 6 | 27.3 |
| **Obesity in family** | | |
| Yes | 16 | 72.7 |
| No | 6 | 27.3 |
| **BMI (Z1)** | | |
| Moderately obese (35-40) | 2 | 9.1 |
| Morbidly obese (41-49) | 16 | 72.7 |
| Super obese (≥50) | 4 | 18.2 |
| **BMI (Z2)** | | |
| 1st degree obese <34 | 13 | 59.1 |
| Moderately obese (35-40) | 7 | 31.8 |
| Morbidly obese (41-49) | 2 | 9.1 |

Preoperative (Z1)
1 year later (Z2)
BMI: Body mass index, SD: Standard deviation

**Table 2.** Comparison of parameters by time

| Variable (n=22) | Z1 | | Z2 | | Statistical analysis* Possibility |
|---|---|---|---|---|---|
| | $\bar{X}$ ± SD | Median (IQR) | $\bar{X}$ ± SD | Median (IQR) | |
| BMI (kg/m$^2$) | 46.83±7.84 | 44.1 [6.5] | 32.59±5.90 | 32.9 [9.3] | Z=-4.107 **p=0.000** |
| Beck depression inventory | 16.18±7.10 | 16.5 [10.0] | 11.86±7.98 | 11.0 [13.5] | t=1.936 p=0.066 |
| Body cathexis scale | 109.64±22.59 | 115.0 [25.0] | 91.41±21.51 | 95.5 [38.5] | t=3.447 **p=0.002** |

*Paired Sample test (t-table value) was used to compare the measurement values of two dependent groups in data with normal distribution, and "Wilcoxon" test (Z-table value) statistics were used in data without normal distribution. Preoperative (Z1), 1 year later (Z2)
BMI: Body mass index, SD: Standard deviation, IQR: Inter quantile range

affected by weight loss and weight regain. There are different biological and psychological ways of explaining the relationship between depression and obesity (19). From a psychological perspective, weight-related stigma, increased body dissatisfaction, and decreased self-esteem are risk factors for depression (45). Also, low weight loss and weight regain after an invasive weight loss treatment such as bariatric surgery can cause feelings of failure and helplessness and increase the risk of depression.

**Study Limitations**

The limitation of the study was that it was performed in a limited number of groups who underwent restrictive bariatric surgery in a single center. The results of this study could only be generalized to the study group. In addition, examining the results one year after bariatric surgery was also within the limitations of the study.

**Table 3.** Comparison of beck depression inventory and body cathexis scale scores according to variables

| | | Z1 | | | | Z2 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | BDI | | BCS | | BDI | | BCS | |
| Variables (n=22) | n | $\bar{X}$ ± SD | Median (IQR) | $\bar{X}$ ± SD | Median (IQR) | $\bar{X}$ ± SD | Median (IQR) | $\bar{X}$ ± SD | Median (IQR) |
| **Age** | | | | | | | | | |
| <30 | 10 | 16.50±8.36 | 16.5 (15.0) | 106.40±22.12 | 115.0 (28.0) | 15.80±8.35 | 15.5 (12.3) | 93.10±22.33 | 95.5 (44.8) |
| 30-40 | 7 | 12.86±4.45 | 12.0 (8.0) | 114.57±15.33 | 121.0 (22.0) | 7.43±7.43 | 5.0 (10.0) | 96.14±19.04 | 104.0 (31.0) |
| >40 | 5 | 20.20±6.14 | 17.0 (11.0) | 109.20±33.99 | 112.0 (54.0) | 10.20±4.21 | 11.0 (6.0) | 81.40±24.35 | 82.0 (41.5) |
| **Statistical analysis*** | | F=1.683 | | F=0.251 | | F=2.826 | | F=0.722 | |
| **Possibility** | | p=0.212 | | p=0.780 | | p=0.084 | | p=0.499 | |
| **Gender** | | | | | | | | | |
| Male | 6 | 16.17±8.66 | 15.5 (13.0) | 96.50±33.60 | 102.5 (68.0) | 10.00±5.93 | 11.5 (10.8) | 82.33±15.50 | 85.5 (27.8) |
| Female | 16 | 16.19±6.74 | 16.5 (12.0) | 114.56±15.59 | 116.5 (20.0) | 12.56±8.69 | 11.0 (17.0) | 94.81±22.96 | 103.5 (43.5) |
| **Statistical analysis** | | t=-0.006 | | t=-1.267 | | t=-0.662 | | t=-1.226 | |
| **Possibility** | | p=0.995 | | p=0.254 | | p=0.516 | | p=0.234 | |
| **Marital status** | | | | | | | | | |
| Married | 11 | 18.09±5.92 | 17.0 (11.0) | 116.45±23.04 | 117.0 (13.0) | 10.18±6.11 | 11.0 (7.0) | 91.82±21.74 | 96.0 (39.0) |
| Single | 11 | 14.27±7.91 | 16.0 (9.0) | 102.82±20.94 | 101.0 (30.0) | 13.55±9.49 | 14.0 (19.0) | 91.00±22.33 | 95.0 (38.0) |
| **Statistical analysis** | | t=1.281 | | Z=-1.610 | | t=-0.988 | | t=0.087 | |
| **Possibility** | | p=0.215 | | p=0.107 | | p=0.335 | | p=0.931 | |
| **Education status** | | | | | | | | | |
| Primary education | 5 | 18.00±6.12 | 16.0 (12.0) | 123.40±17.83 | 117.0 (26.0) | 7.60±8.85 | 3.0 (14.5) | 96.40±25.37 | 107.0 (46.5) |
| Secondary education | 11 | 15.91±9.12 | 16.0 (15.0) | 106.55±21.49 | 114.0 (28.0) | 15.46±7.85 | 14.0 (11.0) | 91.90±17.22 | 95.0 (28.0) |
| High education | 6 | 15.17±3.25 | 17.0 (4.0) | 103.83±26.72 | 108.0 (42.0) | 8.83±4.88 | 10.5 (8.5) | 86.33±27.92 | 80.5 (56.3) |
| **Statistical analysis** | | F=0.216 | | F=1.260 | | F=2.607 | | F=0.284 | |
| **Possibility** | | p=0.807 | | p=0.306 | | p=0.100 | | p=0.756 | |
| **Obesity in family** | | | | | | | | | |
| Yes | 16 | 16.06±6.70 | 16.0 (12.0) | 112.56±20.11 | 116.5 (20.0) | 13.69±8.13 | 11.5 (11.8) | 91.31±22.54 | 90.0 (42.3) |
| No | 6 | 16.50±8.76 | 17.0 (14.0) | 101.83±28.79 | 101.5 (46.0) | 7.00±5.48 | 7.5 (10.8) | 91.67±20.49 | 95.5 (37.8) |
| **Statistical analysis** | | t=-0.126 | | t=0.992 | | t=1.849 | | t=-0.034 | |
| **Possibility** | | p=0.901 | | p=0.333 | | p=0.079 | | p=0.974 | |

*In the data with normal distribution, the "Independent Samplet"-test (t-table value) was used to compare the measurement values of two independent groups, and the "ANOVA" test (F-table value) statistics were used for the comparison of three or more independent groups. The "Mann-Whitney U" test (Z-table value) statistics were used to compare the measurement values of two independent groups in the data that did not have a normal distribution. Preoperative (Z1), 1 year later (Z2). BMI: Body mass index, SD: Standard deviation, IQR: Inter quantile range

**Table 4.** Correlation between weight loss and improvements in psychological variables

| Correlation* (n=22) | | Z1<br>BMI (kg/m²) | Z2<br>BMI (kg/m²) |
|---|---|---|---|
| Beck depression inventory | r | 0.448 | -0.025 |
| | p | **0.036** | 0.913 |
| Body cathexis scale | r | 0.394 | 0.289 |
| | p | 0.069 | 0.192 |

*Pearson correlation coefficient was used in the analysis of the relationships between two quantitative variables with normal distribution, and Spearman correlation coefficient was used in cases where at least one of them did not show normal distribution. Preoperative (Z1), 1 year later (Z2)
BMI: Body mass index

## Conclusion

As a result, it was determined that patients experienced a significant weight loss one year after bariatric surgery, that borderline clinical depression or moderate depression before surgery changed to mild depression one year later, and that bariatric surgery had a positive effect on body image.

Considering the multifactorial characteristics of obesity, a multidisciplinary approach should be used, such as preparing and educating bariatric surgery patients for postoperative life changes. In addition, patients should be evaluated psychiatrically. For bariatric surgery to be successful, it is also important that patients be included in a program that combines recommendations on diet, physical activity, and psychosocial problems both pre- and post-operatively. In addition, new studies with longer follow-up periods are recommended by evaluating the effect of different factors with larger sample groups.

### Ethics

**Ethics Committee Approval:** The study was conducted after obtaining ethics committee approval (date: 23.08.2013, number: 22 decision no: 15) from the Non-Invasive Clinical Research Ethics Committee of Çukurova University Faculty of Medicine and institutional permissions from the hospital where the research was conducted.

**Informed Consent:** The patients who accepted to participate in the study were given detailed information about the study and their written consent was obtained.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Concept: D.G., Ş.Y., D.A., S.E., S.A., Design: D.G., Ş.Y., D.A., S.E., S.A., Data Collection or Processing: D.G., Ş.Y., D.A., S.E., S.A., Analysis or Interpretation: D.G., Ş.Y., D.A., S.E., S.A., Literature Search: D.G., Ş.Y., D.A., S.E., S.A., Writing: D.G., Ş.Y., D.A., S.E., S.A.

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Original Article

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# Can Sepsis-induced Coagulopathy Scores and Routine Blood Tests Indicate Prognosis in Patients with COVID-19?

## Sepsise Bağlı Koagülopati Skoru ve Rutin Kan Testleri COVID-19'lu Hastalarda Prognozu Öngörebilir mi?

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## ABSTRACT

**Objective:** Coronavirus disease-19 (COVID-19) is a multisystemic disease and prognostic factors should be well defined to assess its severity. Sepsis-induced coagulopathy (SIC) score is calculated using parameters related to cardiac, renal, gastrointestinal, and central nervous systems, and coagulation. In this study, we investigated the prognostic effectiveness of the SIC score during the follow-up of patients with COVID-19.

**Methods:** The study was conducted retrospectively by evaluating 123 patients diagnosed as having COVID-19 and hospitalized in the intensive care unit. Patients were divided into two groups, low-risk and high-risk, according to their calculated SIC scores. Patients in these groups were compared in terms of laboratory parameters and outcome patterns.

**Results:** The rate of in-hospital deaths was higher in the group with positive SIC scores compared to the group with negative scores. In the positive-SIC (high-risk) group, albumin level was 2.6±0.6 g/dL, the neutrophil-lymphocyte ratio was 13.6±13.8%, and prothrombin time (PT) was 18.2±2.8. The difference between the values obtained in the comparison between the groups was found to be statistically significant.

**Conclusion:** The SIC score can be used to predict in-hospital mortality in patients wi the COVID-19. Serum albumin level was shown to have a significant association with poor prognosis in our study. An increase in the neutrophil-lymphocyte ratio, which is a cheap, easily measured, and reproducible parameter, can be used as an indicator of poor prognosis. PT was prolonged by 4 seconds over

## ÖZ

**Amaç:** Koronavirüs hastalığı-19 (COVID-19) multisitemik bir hastalıktır ve hastalığın ciddiyetini değerlendirmek için prognostik faktörler iyi tanımlanmalıdır. Sepsise bağlı koagülopati (SIC) skoru; kardiyak, renal, gastrointestinal, merkezi sinir sistemi ve pıhtılaşma ile ilgili parametreler kullanılarak hesaplanır. Bu çalışmada, COVID-19'lu hastaların takibi sırasında SIC skorunun prognostik etkinliğini araştırdık.

**Yöntemler:** Çalışma COVID-19 tanısı konup yoğun bakıma yatırılan 123 hasta değerlendirilerek retrospektif olarak yapıldı. Hesaplanan SIC skoruna göre hastalar düşük riskli ve yüksek riskli olmak üzere iki gruba ayrıldı. Her iki gruptaki hastalar laboratuvar parametreleri ve sonlanım şekilleri (ölen, taburcu) açısından karşılaştırıldı.

**Bulgular:** Hastane içi ölümlerin oranı SIC skoru pozitif olan grupta negatif olan grup ile karşılaştırıldığında daha yüksek bulundu (p<0,001). SIC skoru pozitif hasta grubunda albümin düzeyi 2,6±0,6 g/dL, nötrofil lenfosit oranı %13,6±13,8 ve protrombin zamanı (PZ) 18,2±2,8 idi. Gruplar arası karşılaştırmada elde edilen değerler arasındaki fark istatistiksel olarak anlamlı bulundu.

**Sonuç:** SIC skoru, COVID-19'lu hastalarda hastane içi mortaliteyi tahmin etmek için kullanılabilir. Çalışmamızda serum albümin düzeyinin kötü prognoz ile anlamlı bir ilişkisi olduğu gösterildi. Ucuz, kolay ölçülebilir ve tekrarlanabilir bir parametre olan nötrofil-lenfosit oranındaki artış kötü prognoz göstergesi olarak kullanılabilir. Çalışmamızda PZ normal değerin (10-14 saniye) üzerinde 4 saniye (18,2±2,8 saniye) uzadı. PZ uzaması mortalite ile

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**ABSTRACT**

the normal value in our study. PT prolongation may be associated with mortality. SIC score can serve as a marker of disease severity.

**Keywords:** COVID-19, sepsis-induced coagulopathy score, prognosis

**ÖZ**

ilişkili olabilir. SIC skoru, hastalığın şiddetini gösteren bir belirteç olarak kullanılabilir.

**Anahtar Sözcükler:** COVID-19, sepsise bağlı koagülopati skoru, prognoz

## Introduction

The coronavirus disease-19 (COVID-19), a worldwide pandemic, is a cause of high mortality and morbidity (1). It is a multisystemic disease (2). Since the clinical course of the disease is variable, it is important to evaluate its prognosis (3). The parameters to be used should be inexpensive, easily measurable, and repeatable. Complete blood count, urea, creatinine, lactate dehydrogenase (LDH), creatine kinase (CK), D-dimer, ferritin, troponin, C-reactive protein (CRP), coagulation parameters, and ferritin are routine parameters that are measured in emergency rooms for COVID-19 (4). The Sequential Organ Failure Assessment (SOFA) score evaluates the patients' saturation, blood pressure, consciousness, liver and kidney functions. Sepsis-induced coagulopathy (SIC) score is calculated by adding coagulation and platelet count to the SOFA score. It is important for the feasibility of the study that COVID-19 has a multisystemic effect (5) and that the SIC score includes parameters that will respond to this diversity. SIC is a scoring system that considers coagulation abnormalities in sepsis. It is used for possible sepsis-induced coagulopathy (6). Therefore, we decided to use the SIC score in this study.

In this study, we investigated the prognostic effectiveness of the SIC score during the follow-up of patients with COVID-19. The SIC score and some laboratory markers (albumin, PT, NLR) can serve as early markers of severe disease and can be used to develop prognostic scores.

## Methods

The study was carried out retrospectively in the emergency department between 01.03.2020 and 31.05.2020. It was carried out in accordance with all the criteria set in the Declaration of Helsinki. Data were obtained from hospital records using ICD-10 code U07.3 (COVID-19). Patients over the age of 18 who were diagnosed as having COVID-19 (confirmed by polymerase chain reaction) and hospitalized in the intensive care unit (ICU) were included in the study. Patients excluded from the study are shown in Figure 1. Those whose SIC score could not be calculated due to missing laboratory data were excluded from the study (Figure 1).

The patients were first evaluated in the emergency room and then sent to the ICU. The criteria used for the indication of ICU hospitalization were: dyspnea and severe respiratory distress, respiratory rate ≥30/min, $PaO_2/FiO_2$<300, $SpO_2$<90% or $PaO_2$<70 mmHg despite oxygen therapy, mean arterial pressure <65 mmHg, tachycardia >100/min.

Using these criteria, 123 of 723 patients were included in the study over a three-month period. The SIC score was used to assess the severity of the disease. SIC score was calculated from the blood sample and vital signs taken at the time of first admission to the emergency department. The parameters of this score were platelet count, prothrombin time (PT) and SOFA score. SIC score can be calculated using platelet count, PT or

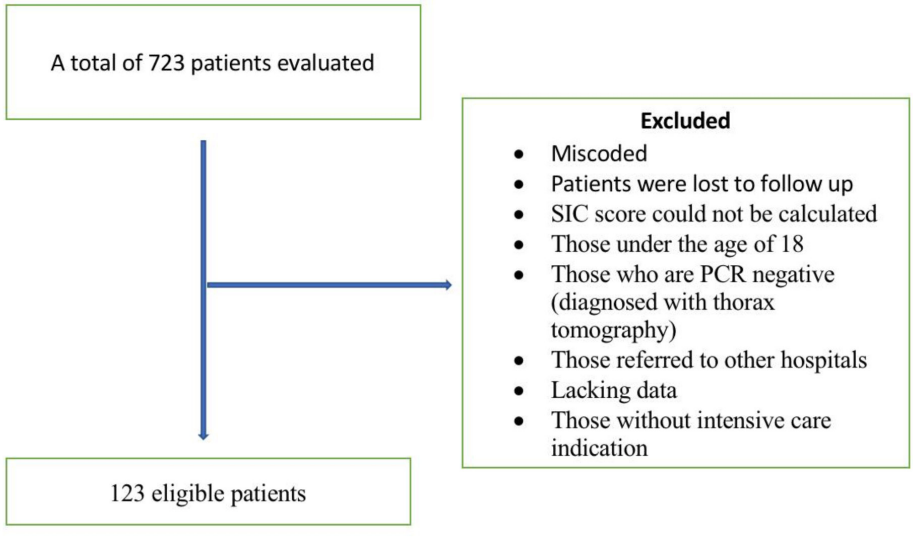


**Figure 1.** Flowchart of patient selection
PCR: Polymerase chain reaction

INR value, SOFA score. Many studies have shown that PT levels present at admission in patients with COVID-19 may be used as early prognostic markers of severe pneumonia requiring transfer to the ICU. So, we used PT instead of INR to calculate SIC score (7). A calculated score of four or more is considered high risk (Table 1). From the results of blood samples taken when the patients presented to the emergency department; complete blood count, urea, creatinine, albumin, LDH, CK, D-dimer, ferritin, troponin, CRP and coagulation parameters were recorded. We divided the patients into two groups: low risk (negative SIC score) and high risk (positive SIC score). Routine blood parameters were compared between the groups. The relationship between SIC score and patient outcomes (death or discharge) was investigated.

### Population and Sample

The research population consisted of patients over the age of 18 who were admitted to the emergency department of our hospital and were diagnosed as having COVID-19. The study was carried out between 01.03.2020 and 31.05.2020. As a result of the power analysis, the values were determined as $\alpha$=0.05, $\beta$=0.20, (1-$\beta$)=0.80, and it was decided to include 123 patients in the sample. The power of the test was evaluated as p=0.89904.

Ethics committee approval with the date 22.12.2020 and decision number 21/407 was obtained from the ethics committee of our university.

### Statistical Analysis

Behaviors of quantitative variables were expressed using centralization and measures of variance: mean ± standard deviation. The chi-square test was used to identify differences in ratios or relationships between categorical variables. To show the behavioral differences of the group averages, the ANOVA and T-test were used in cases where the assumptions of normality and equivalence were met, and the Mann-Whitney U test method was used when the assumption of normality was not met. Statistical significance was determined as being p≤0.05 for all analyses. Statistical analyses were provided with the IBM SPSS (Statistics Package for Social Sciences for Windows, Version 21.0, Armonk, NY, IBM Corp) program package.

## Results

Of the 123 patients evaluated, 72 were male (58.5%) and 51 were female (41.5%). The numbers of female/men with SIC score negative/positive are given in Table 2. The mean age was 70.6±13.8 years. The mean age of those with negative SIC score was 69.5±12.2 years, and of those with positive SIC score was 72±15.9 years (Table 2). The most common chronic diseases were hypertension (69 patients, 56.1%), diabetes mellitus (45 patients, 36.6%), and coronary artery disease (45 patients, 36.6%). There was a statistically significant difference in the numbers of those with heart failure and chronic kidney failure between the high-risk and low-risk groups (Table 2). The most common complaints were shortness of breath (48 patients, 39%) and fever (33 patients, 26.8%). There were 69 patients (56.1%) with a Glasgow Coma score of 14 or less. There were 71 patients (57.7%) with a negative SIC score and 52 patients (42.3%) with a positive score. The compared vital signs of patients with negative and positive SIC scores are given in Table 3. Six of the 20 parameters examined showed a statistically significant difference between the groups. The difference in the values of decrease in albumin level (p=0.003), increase in NLR (p<0.001), and prolongation in PT (p<0.001) between the groups was found to be statistically significant. All checked parameters are shown in Table 4. Six patients (8.5%) with negative SIC score died, and 65 patients (91.5%) were discharged. Twenty five patients (48.1%) with positive SIC score died, and 27 patients (51.9%) were discharged (p<0.001) (Table 5).

## Discussion

In this study, we found that the SIC score is effective in predicting in-hospital mortality in patients with COVID-19. It has been

**Table 1.** Scoring for the diagnosis of SIC and SOFA

| The Sepsis-Induced coagulopathy (SIC) score | | | | |
|---|---|---|---|---|
| Category | **Parameter** | **0 point** | **1 point** | **2 points** |
| Prothrombin time | PT-INR | ≦1.2 | 1.2-1.4 | >1.4 |
| Coagulation | Platelets $10^9$/L | ≧150 | 100-150 | <100 |
| Total SOFA | SOFA four items | 0 | 1 | ≧2 |
| The Sequential Organ Failure Assessment (SOFA) score | | | | |
| Category | **1 point** | **2 points** | **3 points** | **4 points** |
| $SaO_2/FIO_2$ ratio | 221-301 | 142-220 | 67-141 | <67 |
| Platelets $10^3$/L | <150 | <100 | <50 | <20 |
| Creatinine mg/dL | 1.2-1.9 | 2.0-3.4 | 3.5-4.9 | >5.0 |
| Bilirubin mg/dL | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | >12.0 |
| Hypotension | MAP <70 | Dopamine ≤5 or dobutamine (any) | Dopamine >5 or NE ≤0.1 | Dopamine >15 or NE >0.1 |
| GCS score | 13-14 | 10-12 | 6-9 | <6 |

INR: International normalisation ratio, PT: Prothrombin time, SOFA: Sequential Organ Failure Assessment, NE: Norepinephrin, GCS: Glasgow coma score

shown that COVID-19 has serious effects on many systems such as the respiratory, cardiac, renal, gastrointestinal, and central nervous systems (8,9). The reason for this finding may be that COVID-19 is a multisystemic disease and the SIC score contains parameters to evaluate many systems.

Coagulation disorder plays an important role in the clinical process of COVID-19. In particular, a prolongation of PT for more than 3 seconds has been shown to be a strong prognostic factor (10). In our study, PT prolongation was over 4 seconds in the SIC-positive group. Recognition of prolonged PT is essential for early diagnosis of disseminated intravascular coagulability (DIC). It is important to reduce the risk of DIC and predict the need for intensive care in patients with COVID-19.

Low serum albumin level is an important indicator of morbidity and mortality. The condition that causes hypoalbuminemiain COVID-19 is severe inflammation, rather than hepatocellular damage (liver function tests are normal) (11,12). In this study, we found that low albumin level at admission might be associated with mortality. In our study, albumin level was below normal values in both groups, but it was lower in the SIC-positive group (2.6±0.6 g/dL). This difference was statistically significant (p=0.003).

While neutrophil count increases in bacterial infections, lymphocyte count decreases during viremia. Examining these two parameters can greatly aid in the assessment of COVID-19 infection. NLR can be used as an easy-to-calculate, inexpensive, and effective parameter, giving early warning for COVID-19 infection. Such markers are important for early diagnosis and management of the disease. NLR was reported as a prognostic marker in patients with COVID-19 in many previous studies (13,14). In our study, NLR was evaluated and it was found to be 6.5% in SIC-negative patients and 13.6% in SIC-positive patients (p<0.001).

High red cell distribution width (RDW) has been associated with increased mortality in many diseases (such as chronic obstructive pulmonary disease, pneumonia, sepsis, and viral hepatitis) (15,16). In addition, a RDW of over 14% is considered a strong inflammatory marker (17). A high RDW level in viral infections may be due to deregulation of erythrocyte homeostasis and impaired production. Inflammation and oxidative conditions can cause insufficient erythropoiesis deformation. Hyperinflammatory response and cytokine storm determine the clinical process in COVID-19 (18).

In our study, while the RDW was within the normal range in patients with negative SIC score, it increased to 14% in patients with positive SIC score (p=0.035). Therefore, RDW should be part of routine laboratory assessment and monitoring of COVID-19.

**Table 2.** SIC score and chronic disease

| | n (%) | SIC negative n (%) | SIC positive n (%) | p-value (p) |
|---|---|---|---|---|
| Gender | Female 51 (41.5) | 26 (36.6) | 25 (48.1) | 0.27 |
| | Male 72 (58.5) | 45 (63.4) | 27 (51.9) | |
| Age | Mean ± SD | 69.5±12.2 | 72±15.9 | 0.12 |
| Chronic disease | Diabetes mellitus | 24 (33.8) | 21 (40.4) | 0.57 |
| | Hypertension | 36 (50.7) | 33 (63.5) | 0.22 |
| | Heart failure | 11 (15.5) | 19 (36.5) | 0.01 |
| | Hepatic disease | 8 (11.3) | 4 (7.7) | 0.72 |
| | Chronic renal failure | 9 (12.7) | 18 (34.6) | 0.00 |
| | Coronary heart disease | 23 (32.4) | 22 (42.3) | 0.34 |
| | Chronic pulmonary | 21 (29.6) | 12 (23.1) | 0.55 |
| | Malignancy | 8 (11.3) | 7 (13.5) | 0.93 |
| | Cerebrovascular accident | 10 (14.1) | 8 (15.4) | 1.00 |

SIC: Sepsis-induced coagulopathy, SD: Standard deviation

**Table 3.** SIC score and vital signs

| Parameters | SIC negative (n=71) Mean ± SD | SIC positive (n=52) Mean ± SD | p-value (m) |
|---|---|---|---|
| Body temperature °C | 37.1±0.8 | 37.2±0.7 | 0.13 |
| Respiratory rate/minute | 22.3±3.2 | 21.2±2.5 | 0.14 |
| Systolic blood pressure mmHg | 141.9±35.3 | 135.4±34.8 | 0.44 |
| Heart rate/minute | 105.6±29.3 | 94.8±11.8 | 0.11 |

m: Mann-Whitney U test, n: Number, SD: Standard deviation

**Table 4.** SIC score and blood parameters

| Parameters | Unit | SIC negative (mean ± SD) | SIC positive (mean ± SD) | p-value |
|---|---|---|---|---|
| Urea | mg/dL | 69±48.2 | 103.8±62.2 | 0.002* |
| Creatinine | mg/dL | 1.4±0.8 | 1.5±0.9 | 0.888* |
| LDH | U/L | 533.1±791.9 | 701.1±927.1 | 0.052* |
| PT | sec | 16.57±3.3 | 18.2±2.8 | <0.001* |
| PTT | sec | 38.9±11.1 | 41.1±10.2 | 0.29* |
| INR | Ratio | 1.5±0.5 | 1.5±0.6 | 0.184* |
| WBC | $10^9$/L | 9.8±5.5 | 9.8±5.0 | 0.66* |
| Hemoglobin | g/dL | 12.1±2.2 | 11.6±2.1 | 0.194* |
| NLR | % | 6.5±3.9 | 13.6±13.8 | <0.001* |
| Albumin | g/dL | 3.0±0.6 | 2.6±0.6 | 0.003** |
| AST | IU/L | 43.8±9.1 | 59.9±10.5 | 0,166 |
| ALT | IU/L | 34.9±3.3 | 43,8±2.5 | 0,826 |
| RDW | % | 13.1±1.6 | 14.0±2.2 | 0.035* |
| Troponin | ng/dL | 83.5±148.1 | 127.2±246.8 | 0.838* |
| D-Dimer | ng/mL | 950±1318.2 | 1103.5±1026.3 | 0.073* |
| Creatine kinase | U/L | 144.8±124.6 | 196.8±182.2 | 0.154* |
| C-reactive protein | mg/L | 110.23±76.5 | 128.3±71.9 | 0.063* |
| Ferritin | ng/mL | 885.9±885.7 | 1352.2±1435.1 | 0.068* |

LDH: Lactate dehydrogenase, PTT: Partial thromboplastin time, INR: Internationel normalized ratio, WBC: White blood cells, NLR: Neutrophil/lymphocyte ratio, RDW: Red cell distribution width, PT: Prothrombin time, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase. **: Anova T-test, *: Mann-Whitney U test

**Table 5.** Comparison of the patients that died in hospital and those that were discharged

| | | SIC negative n (%) | SIC positive n (%) | p-value |
|---|---|---|---|---|
| Outcomes | Died in hospital | 6 (8.5%) | 25 (48.1%) | <0.001 |
| | Discharged | 65 (91.5%) | 27 (51.9%) | |

p: Pearson chi-squared test, n: Number, %: Percent, SIC: Sepsis-induced coagulopathy

Changes in urea level and platelet count were statistically significant (p=0.002, p=0.014). In addition, the increase in LDH, D-Dimer, CRP and ferritin levels should be monitored more closely (Table 5).

### Study Limitations

One of the most important limitations of our study was that patient data were obtained retrospectively. Another important limitation was that data belonging to only one center were included in the study.

## Conclusion

The SIC score can be used to predict in-hospital mortality in patients with COVID-19. Decrease in albumin level may be associated with poor prognosis. NLR, which is a cheap, easily measured, and reproducible parameter, is an indicator of a prognosis. Caution should be exercised in critically ill patients with a PT prolongation of four seconds or more (18.2±2.8 seconds) from the normal value. SIC score and some laboratory values (albumin, RDW, PT, NLR) can serve as early markers of severe disease and can be used to develop prognostic scores.

### Ethics

**Ethics Committee Approval:** Bezmialem Vakıf University Non-Interventional Research Board (number: E-54022451-050.01.04-1928/date: 22.12.2020).

**Informed Consent:** Retrospective study.

**Peer-review:** Internally and externally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: B.T., Concept: B.T., Design: E.S., Data Collection or Processing: B.T., E.S., Analysis or Interpretation: A.C., Literature Search: B.T., E.S., Writing: E.S.

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

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Original Article

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# Development of a New HPLC Method for the Identification of Allicin and S-allyl Cysteine in Garlic (*Allium sativum L.*) Extracts

## Sarımsak (*Allium sativum L.*) Ekstraktlarında Allisin ve S-allil Sistein Tayini için Yeni Bir HPLC Yönteminin Geliştirilmesi

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## ABSTRACT

**Introduction:** In this study, a new high performance liquid chromatographic method was developed to determine the amount of allicin (AL) and s-allyl cysteine (SAC) in *Allium sativum L.* extracts.

**Methods:** In the method, C18 column (5 µm x4.6 mm x150 mm) was used as the stationary phase at 25 ºC and acetonitrile: water (70:30, v/v) mixture was used as mobile phase with 1 mL/min flow rate. Isocratic elution was applied. The injection volume was 20 µL. Measurements were carried out at 254 nm with ultraviolet detection. Retention times for AL and SAC were 1.1 and 2.4 min, respectively. The method was validated according to International Conference on Harmonization criteria.

**Results:** The limit of detection values for AL and SAC were 0.6 µg/mL and 1.5 µg/mL, respectively. The limit of quantitation values for AL and SAC were 2 µg/mL and 5 µg/mL, respectively. The linearity of the method was between 2-100 µg/mL and 5-30 µg/mL for AL and s-allyl cysteine, respectively. The developed method was also validated and applied to three different trade extracts.

**Conclusion:** This new method, which is quite fast, simple and economical, can be used in the analysis of *Allium sativum L.* extracts, which are named as black garlic in the contents of food supplements.

**Keywords:** Allicin, S-allyl sisteine, *Allium sativum L.,* HPLC-UV, validation

## ÖZ

**Amaç:** Bu çalışmada, *Allium sativum L.* ekstraktlarındaki allisin (AL) ve s-allil sistein (SAS) miktarını belirlemek için yüksek performanslı yeni bir sıvı kromatografik yöntem geliştirilmiştir.

**Yöntemler:** Yöntemde C18 kolonu (5 µm x4,6 mm x150 mm) 25 ºC'de sabit faz olarak ve hareketli faz olarak 1 mL/dk akış hızında asetonitril: su (70:30, v/v) karışımı kullanıldı. İzokratik elüsyon uygulandı. Enjeksiyon hacmi 20 µL idi. Ölçümler 254 nm'de ultraviyole deteksiyon ile gerçekleştirildi. AL ve SAS için alıkonma süreleri sırasıyla 1,1 ve 2,4 dakika idi. Yöntem, Uluslararası Harmonizasyon Topluluğu kriterlerine göre valide edildi.

**Bulgular:** AL ve SAS için tespit değerlerinin limiti sırasıyla 0,6 µg/mL ve 1,5 µg/mL idi. AL ve SAS için miktar tayini değerlerinin sınırı sırasıyla 2 µg/mL ve 5 µg/mL idi. Yöntemin doğrusallığı AL ve SAS için sırasıyla 2-100 µg/mL ve 5-30 µg/mL arasındaydı. Geliştirilen yöntem ayrıca doğrulanmış ve üç farklı ticari ekstreye uygulandı.

**Sonuç:** Oldukça hızlı, basit ve ekonomik olan bu yeni yöntem, gıda takviyelerinin içeriklerinde siyah sarımsak olarak adlandırılan *Allium sativum L.* ekstraktlarının analizinde kullanılabilir.

**Anahtar Sözcükler:** Allisin, S-allil sistein, *Allium sativum L.,* HPLC-UV, doğrulama

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## Introduction

Secondary metabolites, unlike primary metabolites, are not directly related to the essential vital activities of the plant. Adapting to the environment, pollination, competition, protection from pesticides and continuing its generations are the functions of secondary metabolites. Secondary metabolites are divided into three large classes: phenolic compounds, alkaloids and terpenes (1-2). Compounds containing sulphur, which have a similar effect to secondary metabolites, have been recently the subject of increased research (3).

Garlic (*Allium sativum L.*), belonging to the family *Liliaceae* (*Asphodelaceae*), is a bulbous flowering species of the genus Allium. Garlic, a spice preferred by people for many years, grows naturally in Central Asia and northeastern Iran and is widely used in the world. It is also utilized in Turkey as a food flavoring agent as well as a traditional medicine (4). The previous researches prove that garlic has anti-bacterial, anti-mycotic, anti-spasmodic, anti-diabetic, anti-oxidant, anti-cancer, anti-hyperlipidemic, hypotensive, vasodilator, anti-viral, fibrinolytic activity enhancing, thrombocyte aggregation slowing, anti-hepatoxic, and anti-atherosclerotic effects (5-10). It is used externally in wound healing and in the treatment of ear infections (11).

After the discovery of allicin (AL) (Figure 1) in 1994, many sulfur-containing compounds (allyin, s-allyl cysteine, diallylsulfide, allymercaptan) were identified in garlic. In recent studies, it has been reported that the amino acid s-allyl cysteine (SAC) (Figure 2), which contains a sulfur atom derived from garlic, has many biological activities. SAC is generally used as an alternative to AL in supplementary food preparations. The reason for this is that the AL has a pungent odor (12,13).

Up to date, to determine AL, SAC and bioactive sulfur compounds isolated from garlic (*Allium sativum* L.); high performance liquid chromatography-ultraviolet detector (HPLC-UV) (14,15), high performance liquid chromatography-electrochemical detector (16) and high performance liquid chromatography-mass spectrometry (17) methods have been used. However, there is no developed and validated method in the literature that enables the detection of AL and SAC in pharmaceutical preparations and nutraceuticals and dietary supplements. In addition, there is no method in the literature that quantitates AL and SAC simultaneously.

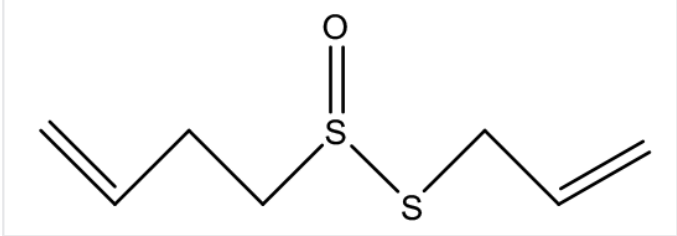


**Figure 1.** Chemical structure of AL
*AL: Allicin*

The aim of this study is to quantify the amount of AL and SAC in nutraceuticals and dietary supplements and extracts containing garlic; it is intended to validate an HPLC technique that will enable selective and sensitive analysis. The developed method does not require any derivatization and time consuming pretreatment procedure. Moreover, it is possible to carry out the separation process with a simply prepared mobile phase in isocratic elution profile rather than a complicated gradient procedure. The detection is also provided easily with UV detection that is used frequently in routine laboratories.

## Method

### Chemicals and Reagents

The AL and SAC were acquired from Sigma Aldrich, St. (Louis, Missouri, United States). Ethanol, methanol and acetonitrile of the HPLC category were obtained from Merck, Darmstadt, Germany. Water was treated through the Human Water systems made in Korea.

### Solutions

The AL primary solution (10 µg/mL) concentration was prepared in ethanol: water mixture (7:3 v/v). SAC primary solution (100 µg/mL) concentration was prepared in ethanol: water mixture (10:10 v/v). These solutions were diluted with ethanol to give standard solutions of 2-100 µg/mL for both analytes.

### Sample Preparation

In order to analyze AL and SAC in garlic (*Allium sativum L.*) extracts, various pretreatment procedures were carried out by dissolving the extracts in different solvents. Extracts were prepared by selecting the most suitable solvent where the dissolution was the best without interference from other components of the extract. Acetonitrile:water (7:3 v/v) was the most suitable solvent system to prepare the sample for chromatographic conditions. Because the sample was dissolved by this system as the best.

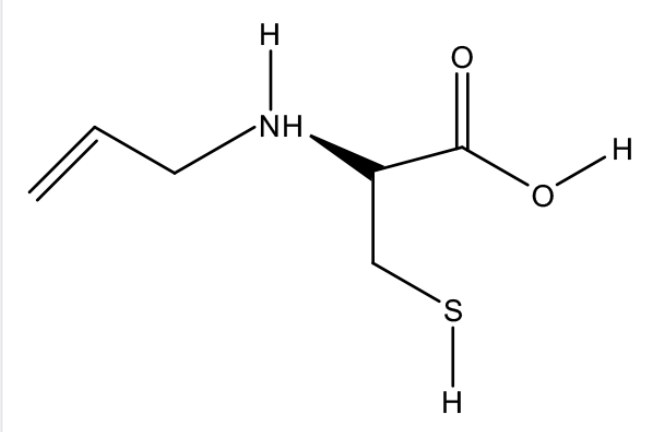


**Figure 2.** Chemical structure of SAC
*SAC: S-allyl cysteine*

### Instrumentation

Spectrophotometric measurements of AL and SAC were made using the Shimadzu UV-160, a 1 cm glass cell spectrophotometer. HPLC tests were performed on a Shimadzu (Japan) LC 20 liquid chromatograph consisting of a LC-20AT pump, SIL AH-HT autosampler part, a SPD-20A HT UV spectrophotometric detector, which was set at 254 nm and CTO 10 AC column oven. The best separation was obtained as a result of experiments with various mobile phase and column types, different flow rates and different detector wavelengths.

### Statistical Analysis

Power analysis was performed to determine the number of garlic extracts. The outcomes were presented as means ± standard deviation (n=3 per each test sample).

## Results

### Chromatographic process

Chromatographic conditions were performed at 25 ºC isocritically on a C18 (150 mm x4.6 mm x5 µm) (Shim-Pack, Shimadzu Corporations-Japan) column. The mobile phase consisted of a mixture acetonitrile and water (70:30, v/v). The experiment was done with a flow rate of 1 mL/min. 20 µL of the analytes was injected into the column.. The chromatograms of the *Allium sativum L.* extracts samples are given in Figure 3.

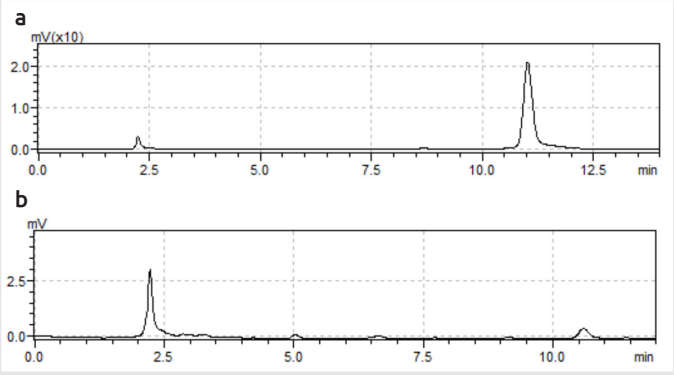


**Figure 3. a)** AL peak in garlic extracts, **b)** SAC peak in garlic extracts

*AL: Allicin, SAC: S-allyl cysteine*

### The Calibration Graph

Calibration graph for AL was constructed by analysis of standard AL solutions at 8 different concentrations between 2-100 µg/mL. Calibration curve for SAC was prepared by analysis of standard SAC solutions at 5 different concentrations between 5-30 µg/mL. Regression equations of the AL and SAC were y=4762.2x-1367.6 (correlation coefficient =0.9959) and a y=874.61x-69.973 (correlation coefficient =0.9967) respectively.

### Validation Parameters of the Method

The newly technique was validated according to the criteria presented by the International Conference on Harmonization (18).

**Parameter of Sensitivity:** The formula limit of detection (LOD) or limit of quantification (LOQ)=kSDa/b was used to compute the LOD and LOQ, where k=3 for LOD and 10 for LOQ, SDa was the standard deviation of the intercept, and b was the slope. As stated in Table 1; LOD and LOQ results for AL were 0.6 and 2 µg/mL, respectively.

**Accuracy, Precision and Recovery:** For the determination of AL in garlic extracts; quality control (QC) samples were prepared in several concentrations (2, 50 and 100 µg/mL) which could be categorized as low, medium and high concentration levels (n=3). For SAC determination; likewise, three different concentrations (5, 15 and 30 µg/mL) of QC samples were prepared (n=3). The accuracy was indicated by the recovery values and the accuracy of the recovery study was determined by the relative standard deviation (RSD) values of the recovery results in six repeated studies. The accuracy of the proposed method was quantified with standard addition technique by spiking QC specimens of standard AL and SAC solutions to garlic extracts including 15 µg/mL of AL and SAC. Absolute recovery of AL and SAC from garlic extracts, removal of AL and SAC from extracts, and comparison of peak areas got from the equal proportions of aqueous non-extracted AL and SAC solutions were examined and evaluated. The average absolute recoveries of AL and SAC were 87% and 90%, respectively. The calculated recovery was 101.55%. In order to determine the precision; three QC samples from each concentration were analyzed on the same day at different hours for intraday analysis and on 3 different days for interday analysis. In intraday tests, the RSD values for

**Table 1.** Results of analytical parameters for the proposed method

| Parameter | Allicin | S-allyl cysteine |
|---|---|---|
| Linearity range* (µg/mL) | 2-100 | 5-30 |
| Regression equation | y=4762.2x-1367.6 | y=874.61x-69.973 |
| Slope ± SD | 4762.2±1.57 | 874.61±1.23 |
| Intercept ± SD | 1367.6±5.66 | 69.973±0.38 |
| Correlation coefficient, $r^2$ | 0.9959 | 0.9967 |
| LOD (µg/mL) | 0.6 | 1.5 |
| LOQ (µg/mL) | 2 | 5 |

*n=5 correspond to replicate analysis for each level.
SD: Standard deviation, LOD: Limit of detection, LOQ: Limit of quantification

AL and SAC were lower than 1.21 and 5.22, respectively. The RSD values of the inter-day results for AL and SAC were lower than 1.18 and 6.32, respectively. Table 2 and Table 3 indicate the recovery and RSD values of recovery.

**Parameter of Robustness:** Robustness studies were done by making minor changes to the method such as flow rate of the mobile phase and the column temperature. The mobile phase ratios were altered from (70:30 v/v) (acetonitrile-water) to 60:40 and 80:20; temperature was altered from 20 ºC to 30 ºC; and the flow rate was altered from 0.8 to 1.2 mL/min. These changes did not have a substantial effect on the system suitability parameters. RSD values were 4.73 and 3.76, respectively, as a result of the change of flow rate and mobile phase ratio. Table 4 illustrates the robustness finding.

**Parameter of Stability:** The working stability of AL and SAC substances was trialed in different storage conditions (at room temperature in the dark for 48 hours and under automatic sampling conditions for 4 ºC for 1 month) for long and short periods of time. In stability studies, it was found that the specimen were kept stable at room temperature for 48 hours and at 4 ºC for 1 month. For all of these trials, the highest RSD percent was 4.12 percent. AL and SAC were stable under all these conditions.

**Application of the Method to the Determination of AL and SAC from Garlic *(Allium sativum* L.*)* Extracts**

The solvent system that best dissolved AL and SAC from garlic *(Allium sativum* L.*)* extracts and was also the most suitable for chromatographic conditions was determined as ethanol:water (7:3). In order to analyze AL and SAC in *Allium sativum* L. extracts taken from 3 different commercial sources, it was developed after dissolving it in an ethanol:water (7:3) solvent system and filtering it through 0.45 µm membrane filters then studied under chromatographic conditions. The relative amounts of SAC contained in the extracts were determined as 68%, 60% and 58%, respectively. AL could not be detected in any of the analyzed extracts. This indicated that AL in these

**Table 2.** Results of recovery studies by standard addition method for S-allyl cysteine

| | Amount present (µg/mL)[a] | Amount added (µg/mL) | Total amount found[b] (µg/mL) (mean ± SD) | Recovery (%) | RSD (%) | RSD of intraday variation (%) | RSD of interday variation (%) |
|---|---|---|---|---|---|---|---|
| | | 5 | 15.68±0.02 | 104.5 | 0.13 | 0.78 | 6.12 |
| S-allyl cysteine | 10 | 15 | 23.96±0.05 | 95.84 | 0.21 | 1.16 | 5.67 |
| | | 30 | 41.5±0.11 | 103.75 | 0.27 | 1.18 | 6.32 |

Mean relative recovery=101.36
SD: Standard deviation, RSD: Relative standard deviation

**Table 3.** Results of recovery studies by standard addition method for allicin

| | Amount present (µg/mL)[a] | Amount added (µg/mL) | Total amount found[b] (µg/mL) (mean ± SD) | Recovery (%) | RSD (%) | RSD of intraday variation (%) | RSD of interday variation (%) |
|---|---|---|---|---|---|---|---|
| | | 2 | 22.31±0.42 | 101.41 | 3.21 | 0.36 | 4.83 |
| Allicin | 20 | 50 | 68.9±0.35 | 98.43 | 3.56 | 1.45 | 4.78 |
| | | 100 | 115.6±0.57 | 96.33 | 4.12 | 1.21 | 5.22 |

Mean relative recovery=98.72
SD: Standard deviation, RSD: Relative standard deviation

**Table 4.** Robustness of the method

| Condition | Value | Recovery % | RSD % |
|---|---|---|---|
| Flow rate mL/min | 0.8 | 94.26 | 4.73 |
| | 1.2 | 97.83 | 6.38 |
| Mobile phase ratio (acetonitrile:aqueous phase) | 60:40 | 103.76 | 3.76 |
| | 80:20 | 96.83 | 5.37 |
| Column temperature | 20 | 96.32 | 3.17 |
| | 30 | 103.24 | 5.28 |

n=3 for all quality control sample levels
RSD: Relative standard deviation

samples was completely fermented into SAC or that there was some unfermented AL below the LOD (0.6 μg/mL).

## Conclusion

The medical effects of garlic (*Allium sativum L.*), especially antioxidant and antimicrobial activities, have been known for centuries. However, it is often not preferred due to the pungent smell of garlic. Therefore, consumption of fresh garlic by fermenting AL to SAC has become popular and fermented garlic preparations (extracts) have begun to appear in the market. In the literature, no method has been found that determines AL and SAC simultaneously. Existing methods for individual assays also include applications such as derivatization step and gradient elution mode. The method we have developed is quite simple, fast and low cost. The method does not require any derivatization reaction, it provides simple mobile phase with isocratic flow. A detection available in routine laboratories, such as UV detection, is used and has very sensitive and selective features.

### Ethics

**Ethics Committee Approval:** This article does not contain any studies with human participants or animal performed by any of the authors.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Concept: G.T., B.C., Design: G.T., B.C., Data Collection or Processing: G.T., B.C., Analysis or Interpretation: G.T., B.C., Literature Search: G.T., B.C., Writing: G.T., B.C.

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

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Original Article

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Bezmialem Science 2023;11(2):200-6

# Relationship Between Plasma Chemerin Levels and Supraventricular Tachycardia

## Plazma Chemerin Seviyeleri ile Supraventriküler Taşikardi Arasındaki İlişki

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### ABSTRACT

**Objective:** Epicardial adipose tissue is the local energy source for the contraction activity of the heart. However, chemerin is a novel chemoattractant adipocytokine released from adipose tissue. Chemerin and its receptor have been detected in epicardial adipose tissue and cardiomyocytes. The relationship between chemerin and cardiovascular diseases such as hypertension, diabetes, obesity, dyslipidemia, coronary heart disease, and atrial fibrillation has been demonstrated in previous studies. As the causes of supraventricular tachycardia (SVT), which is one of the many types of arrhythmias, are still clearly unknown, SVT is still an important source of life-threatening morbidity. In the present study, the purpose was to determine possible relations between plasma chemerin level, which had relation with cardiovascular diseases, with SVT.

**Methods:** A total of 62 patients, who were diagnosed as having SVT by the cardiology clinic, and 27 controls were included in this study. Hematological and serum biochemistry parameters were analyzed. The plasma chemerin concentrations were measured with the ELISA technique.

**Results:** Chemerin levels were higher at statistically significant levels in SVT group compared to the control group ($p<0.001$). The heart rate per minute was significantly lower in the control group compared to the patient group ($p<0.001$). The Pearson's correlation analysis revealed that there was a positive correlation between chemerin levels in plasma and average heart rate. Also, neutrophil/lymphocyte ratio was significantly higher in SVT group than in the control group (1.95±26.53 vs. 1.42±0.7, $p<0.01$).

### ÖZ

**Amaç:** Epikardiyal yağ dokusu, kalbin kasılma aktivitesi için lokal enerji kaynağıdır. Bununla birlikte, chemerin, yağ dokusundan salınan yeni bir kemoatraktan adipositokindir. Chemerin ve reseptörü epikardiyal yağ dokusunda ve kardiyomiyositlerde tespit edilmiştir. Hipertansiyon, diyabet, obezite, dislipidemi, koroner kalp hastalığı ve atriyal fibrilasyon gibi kardiyovasküler hastalıklar ile chemerin arasındaki ilişki önceki çalışmalarda gösterilmiştir. Birçok aritmi tipinden biri olan supraventriküler taşikardinin (SVT) nedenleri hala net olarak bilinmediğinden, SVT hala hayatı tehdit eden önemli bir morbidite kaynağıdır. Bu çalışmada kardiyovasküler hastalıklarla ilişkisi olan plazma chemerin düzeylerinin SVT ile olası ilişkilerinin belirlenmesi amaçlanmıştır.

**Yöntemler:** Bu çalışmaya kardiyoloji kliniği tarafından SVT tanısı konulan toplam 62 hasta ve 27 kontrol dahil edildi. Hematolojik ve serum biyokimya parametreleri analiz edildi. Plazma chemerin konsantrasyonları ELISA tekniği ile ölçüldü.

**Bulgular:** Chemerin düzeyleri kontrol grubuna göre SVT grubunda istatistiksel olarak anlamlı düzeylerde daha yüksekti ($p<0,001$). Dakikadaki kalp hızı, kontrol grubunda hasta grubuna göre anlamlı derecede düşüktü ($p<0,001$). Pearson korelasyon analizi, plazmadaki chemerin seviyeleri ile ortalama kalp hızı arasında pozitif korelasyon olduğunu ortaya koydu. Ayrıca nötrofil/lenfosit oranı SVT grubunda kontrol grubuna göre anlamlı derecede yüksekti (1,95±26,53 vs. 1,42±0,7, $p<0,01$).

**Sonuç:** Bu çalışma ilk kez SVT'de plazma chemerin düzeylerinin yüksek olduğunu gösterdi. Ayrıca bu çalışma yüksek plazma

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## ABSTRACT

**Conclusion:** This study showed for the first time that plasma chemerin level was elevated in SVT. In addition, this study determined a positive correlation between high plasma chemerin concentration and heart rate. Determining and controlling the circulating level of chemerin, which is associated with cardiovascular diseases, inflammation, metabolic syndrome and many other diseases, may be important in SVT.


**Keywords:** Supraventricular tachycardia, chemerin, arrhythmia, cardiovascular diseases


## ÖZ

chemerin konsantrasyonları ile kalp atım hızı arasında pozitif bir korelasyon olduğunu belirledi. Kardiyovasküler hastalıklar, enflamasyon, metabolik sendrom ve daha birçok hastalıkla ilişkisi bulunan chemerinin dolaşımdaki seviyelerini belirlemek ve düzeylerini kontrol etmek SVT'de önemli olabilir.


**Anahtar Sözcükler:** Supraventriküler taşikardi, chemerin, aritmi, kardiyovasküler hastalıklar

## Introduction

Supraventricular tachycardia (SVT) is a general term that is used for all tachycardias that originate from above the atrioventricular node. Arrhythmias, such as atrioventricular nodal reentrant tachycardias (AVNRT), atrioventricular reentrant tachycardias (AVRT), which are caused by various accessory pathway-mediated mechanisms, Atrial Tachycardia, and sinus tachycardias, which are caused by single and multi-focal mechanisms, and atrial flutter and atrial fibrillation are also included in Supraventricular Tachycardias. Paroxysmal SVT is the term used for the subset of SVT, including AVNRT, AVRT, and AT, which have a sudden onset (1).

The anatomical basis of the pathophysiology of SVT (AVRT, AVNRT) is still not known, and the specific abnormalities of the special transmission system have still not been elucidated. However, it should be considered that some types, such as atrial fibrillation and atrial flutter, have more complex pathological backgrounds (2). Many hypotheses have been speculated to explain the etiology of SVT, including the possibility that inflammatory condition triggers arrhythmia (3). It has been foreseen in limited studies that systemic inflammation markers, such as total leukocyte count and subtypes, e.g. neutrophil, lymphocyte, and neutrophil/lymphocyte ratio (NLR), can be used to diagnose SVT (4).

The epicardial fat, which appears as a result of the accumulation of the visceral fat around the heart, plays roles in atrial arrhythmogenesis with its ability to produce and excrete a large number of adipocytokines as an ectopic fat storage with endocrine and inflammatory features near the atrium (5). The plasma level of chemerin, which is an adipocytokine excreted by the epicardial adipose tissue, is elevated in atrial fibrillation. However, chemerin also regulates inflammatory response by affecting the calcium homeostasis, connexins, and atrial electrophysiology in cardiac tissue (6).

Although there are very few studies showing relation between SVT and NLR, there are no studies showing relation between plasma chemerin levels and SVT. The purpose of this study was to search for relation between chemerin levels in the circulation of patients with SVT and possible arrhythmogenic effects of chemerin, and to suggest a useful marker that could be used in the diagnosis and that could be added to clinical parameters.

## Methods

### Patient Population

A total of 62 patients, who were diagnosed as having SVT and admitted to the Cardiology Clinic of Afyonkarahisar Health Sciences University, Faculty of Medicine between November 2019 and November 2020, were included in our study. These participants were matched in terms of age, gender, and ethnicity with 27 healthy adults who had no palpitation symptoms and arrhythmic disease, and who had normal physical examination results, and who were admitted to the adult cardiology clinic for examinations. G*Power 3.1.9.7 was used to calculate the minimum number of participants required to observe a significant difference between two groups at $p<0.05$ (two-tailed test). To obtain a statistical power of 80 for a medium effect size (Cohen's d=.65) a total of 90 participants were required. Individuals with narrow QRS tachycardia documented by electrocardiography and SVT documented electrophysiologically were included in the SVT group. All patients with SVT included in the study had AVRT, AVNRT or AVRT. However, since atrial fibrillation and atrial flutter had different clinical evaluations, they were not included in our study.

Oral and written informed consent forms were received from all patients and healthy volunteers who participated in the study after receiving the approval of the ethics committee for the study (2019/350). Patients with coronary artery disease, heart failure, suspected myocarditis, pericarditis, unstable angina pectoris, ST segment depression due to myocardial infarction, impaired kidney functions (i.e. creatinine levels >1.4 mg/dL), autoimmune disease, acute or chronic hepatic or hepatobiliary disease, pulmonary hypertension, or any malignant history were excluded from the study. Standard 12-lead ECGs were performed for all subjects during the registration.

### Blood Sampling and Laboratory Methods

Blood samples were collected after 12 hours of fasting after admission to the hospital. Five mL venous blood samples were taken from all individuals, centrifuged for 15 minutes at 1,000 rpm in cooled centrifuge device, plasmas were separated, and were then stored at -70 ºC until the analyses were performed. Total and differential leukocyte counts and routine biochemical and hematological tests were performed in line with the

procedures. Furthermore, the distributions of hemogram and full biochemistry parameters in all patients and controls were examined.

**Measurement of Plasma Chemerin Levels**

Plasma chemerin level was examined with a commercially available enzyme immunoassay kit (Bioassay Technology Laboratory, Shanghai, China) in line with the instructions of the manufacturer. The absorbance reading of the samples was carried out with the Chromate 4,300 brand ELISA Reader Device (Awareness Technology, Inc. Martin Hwy, Palm City, USA). The mean values that were obtained with duplicated tests on the samples were given as ng/L.

**Statistical Analysis**

Categorical variables were presented as numbers and percentages, and were compared with the chi-square test. Continuous variables were expressed as mean and SD. The intergroup continuous variables that had normal distribution were compared by using the Independent Samples T-test, or those that did not show normal distribution were compared with the Mann-Whitney U test. The Pearson chi-square analysis was made to evaluate the independent predictors of SVT. Statistical analyses were made with the Statistics Program for Social Sciences (SPSS 15.0. Inc. Chicago, Illinois, USA), and $p<0.05$ was considered as statistically significant.

## Results

The main characteristics of the patients included in the study are summarized in Table 1. No significant difference was detected between the patient group and the control group in terms of gender, age and major risk factors (i.e. hypertension, diabetes mellitus, cerebrovascular accident, dyslipidemia, smoking history). Also, no statistically significant difference was detected in terms of body mass index (BMI), body surface area, and systolic blood pressure measurements aside from hematological and biochemical measurements such as lymphocyte, leukocyte and platelet counts, and blood urea nitrogen, glucose, triglyceride, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), potassium, sodium, chlorine, thyroid stimulating hormone, T3, and T4 levels ($p>0.05$). However, statistically low-level and significant differences were detected in terms of calcium levels in the patient group compared to the control group ($p<0.01$). There was a statistically significant difference in terms of chemerin level in the SVT group compared to the control (SVT group; 485±143.40 and control group; 293±22.85, $p<0.001$) (Table 1, Figure 1). Heart rate per minute was significantly higher in the SVT group than in the control group ($p<0.001$); and a positive correlation was detected between chemerin level in plasma and average heart rate. Figure 2 shows a positive correlation between chemerin level and heart rate in all patients participating in the study ($r=0.279$, $p<0.01$). Although the neutrophil count was significantly higher in the SVT group than in the controls (4.41±2.01, 3.74±1.26, $p<0.001$), lymphocyte count was lower without reaching a statistically significant level in the SVT group than in the control group (2.42±0.93, 2.44±0.81, $p>0.05$). As a result, the NLR, which was one of the independent predictors of SVT, was higher in the SVT group compared to the control group (1.95±26.53, 1.42±0.7, $p<0.01$). However, although platelet lymphocyte ratio (PLR) and C-reactive protein (CRP) level, which were among the other inflammation markers, were higher in the patient group, this was not statistically significant (Table 2).

## Discussion

Epicardial adipose tissue is an ectopic fat storage near the atrium, and can play roles in cardiac pathophysiology with its endocrine and inflammatory features (5). Adipocytokines that are released from this area can have paracrine effects and affect myocardial functions and the incidence of atrial and ventricular arrhythmias due to the proximity of epicardial fat to neuronal plexus and cardiomyocytes (7). The coronary perivascular adipose tissue, which is a part of the epicardial adipose tissue, is defined as the adipose tissue that surrounds the coronary arteries or the perivascular adipose tissue (PAT) (8). Chemerin is mostly produced in the visceral adipose tissue, liver, lungs, heart, ovaries, kidneys, pancreas, and in the placenta albeit in lower amounts (9-12).

Recent studies show that elevated chemerin concentration in the serum is positively correlated with obesity, dyslipidemia, insulin resistance, hypertension, diabetes, coronary artery disease, and renal failure (13). Elevated chemerin level in the circulation is also positively associated with various factors of the metabolic syndrome, such as high glucose level in the circulation, high triglyceride level, low HDL level, high LDL level, and BMI (10,14-16). When considered with a clinical viewpoint, chemerin level in the circulation also has positive correlations with inflammation markers such as CRP. The risk of development of metabolic syndrome and also cardiovascular diseases is increased in obese patients as they have ten-fold more chemerin in their circulation when compared with healthy individuals (17).

SVT is a common and rapid arrhythmia type in patients who do not have organic heart disease, and is caused by electrical stimuli originating from above the ventricles of the heart (18). In line with the Coumel Theory, three elements are needed for clinical arrhythmia development. These three elements are an anatomically-evolving ectopic accessory pathway, a triggering factor, and a modulator caused mostly by the autonomous nervous system (19). Although triggering factors are still a matter of debate, and although it may often be an extrasystole pulse, it is still unclear what causes SVT (20).

Heart rhythms stem from the electrical activity generated by the opening-closing of the ion channels in cardiomyocytes. The opening of the voltage-gate sodium channel initiates the spread of an electrical action potential promoting the cellular depolarization and coordinated contraction of the heart. The change in the function of the ion channel is associated with a wide range of cardiac transmission pathologies such as arrhythmias (21). Voltage-gate sodium channels are expressed at high rates in all types of cardiac myocytes, in sinus node, transmission pathways,

and in atrial and ventricular myocytes (22). The ion distributions of the sodium, potassium, and calcium ions inside-outside the cell, which contribute primarily to membrane potential, change the membrane potential. For this reason, abnormalities that occur in the formation of the action potential not only affect the contraction power of the heart, but also the rate at which the heart beats per minute (23). Yamamoto et al. (24) conducted a study and showed that acute intra-cerebral chemerin-9 injection increased systemic blood pressure, and also that the treatment of chemerin CMKLR1 receptor with siRNA eliminated this effect. In their study, although they were unable to identify a specific nucleus and/or cells that were associated with the elevation of the blood pressure, they speculated that chemerin might cause projection in the cardiovascular center with voltage-gate sodium channels and peripheral sympathetic nervous system activation. The endogenous chemerin coming from the PAT such as leptin adipocytokine strengthens the effects of the sympathetic nerve function (25). However, current studies showing that chemerin

**Table 1.** Basic demographic, hematological, and biochemical characteristics of the study population

| Variable | Patient | | Control | | |
|---|---|---|---|---|---|
| | Mean/median | SD | Mean/median | SD | P |
| Female, n (%) | 35 F (56.5%)<br>27 M (43.5%) | | 13 F (48.1%)<br>14 M (51.9%) | | 0.4** |
| Age (year) | 56.38 | 14.64 | 57.64 | 10.23 | 0.69 |
| Body mass index, kg/m$^2$ | 28.90 | 4.81 | 29.47 | 6.69 | 0.6 |
| Body surface area | 1.94 | 3.4 | 1.88 | 0.1 | 0.08* |
| Systolic BP, mm/Hg | 131.5 | 11.86 | 128.46 | 10.26 | 0.2 |
| Diastolic BP, mm/Hg | 79.20 | 13.33 | 72.79 | 10.25 | **0.01** |
| Heart rate | 84.31 | 11.96 | 74.07 | 9.99 | **0.000** |
| Neutrophil count (10$^3$/µL ) | 4.41 | 2.01 | 3.74 | 1.26 | **0.001*** |
| Lymphocyte count (10$^3$/µL) | 2.42 | 0.93 | 2.44 | 0.81 | 0.95 |
| Leukocyte count (10$^3$/µL) | 8.16 | 2.27 | 7.77 | 2.14 | 0.44 |
| Platelet count (10$^3$/µL) | 278.17 | 84.57 | 254.51 | 73.31 | 0.21 |
| BUN (mg/dL) | 15.23 | 8.17 | 12.85 | 6 | 0.29* |
| Fasting glucose (mg/dL) | 98.50 | 23.09 | 103 | 47.82 | 0.12* |
| Total cholesterol (mg/dL) | 172.8 | 41.76 | 177.70 | 38.62 | 0.61 |
| HDL (mg/dL) | 46.00 | 40.02 | 39.35 | 11.67 | 0.4 |
| LDL (mg/dL) | 112.92 | 35.26 | 109.09 | 36.09 | 0.6 |
| Potassium, level | 4.54 | 0.4 | 4.63 | 0.3 | 0.31 |
| Calcium, level | 9.21 | 0.64 | 9.58 | 0.55 | 0.01 |
| Sodium level | 139.80 | 3.1 | 135.11 | 24.75 | 0.33 |
| Chlorine level | 102.66 | 3.67 | 101.59 | 2.74 | 0.18 |
| TSH (mIU/L) | 1.47 | 1.19 | 1.42 | 0.95 | 0.7* |
| T3 (mIU/L) | 2.87 | 0.63 | 2.95 | 0.49 | 0.52 |
| T4 (mIU/L) | 1.29 | 0.25 | 1.35 | 0.2 | 0.23 |
| Chemerin ng/L | 485 | 143.40 | 293 | 22.85 | 0.000 |
| Hypertension, n (%) | 31 (50%) | | 13 (48.1%) | | 0.8 |
| Diabetes, n (%) | 9 (14.5%) | | 9 (33.3%) | | 0.06** |
| SVO, n (%) | 2 (3.2%) | | - | | 0.34** |
| Dyslipidemia, n (%) | 5 (8.1%) | | 2 (7.4%) | | 0.9** |
| Beta blocker, n (%) | 38 (61.3%) | | 10 (37%) | | **0.03**** |
| ACEI treatment, n (%) | 25 (40.3%) | | 8 (29.6%) | | 0.3** |
| Smoking, n (%) | 24 (38.7%) | | 11 (40.7%) | | 0.8** |

*Mann-Whitney U test, **Chi-square ($x^2$) test, Independent Samples t-test were used for other parameters.
SD: Standard deviation, BP: Blood pressure, HDL: High density lipoprotein, LDL: Low density lipoprotein, TSH: Thyroid stimulating hormone, SVO: Cerebrovascular event

induces L-type calcium channel activation, (26) and that L-type calcium channel reduces mRNA expression level (27) also show that chemerin can participate in intracellular ion regulation after modifying the function and structure of calcium channels. It was found in our study that calcium level was lower in the SVT group than in the control group. Extracellular low ionized calcium level increases the ion channel's permeability to sodium ion, causing progressive depolarization and increases the probability of action potential as a result of calcium ions' interaction with the outer surface of sodium channels in the plasma membrane of the nerve cells. It increases the potential for resting effectively, in other words, make cells more prone to be stimulated (28).

In a study conducted with patients who had atrial fibrillation, increased chemerin level was detected in circulation. It was determined in the same study that patients with permanent atrial fibrillation had higher chemerin level when compared to patients with persistent and paroxysmal atrial fibrillation (29). There are no studies supporting that chemerin affects heart rate directly. However, another study reporting that heart rate decreased unexpectedly in rats of which chemerin gene was knocked-out supported that there might be an interaction between chemerin level and heart rate (30). Based on the literature data mentioned so far, it can be argued that chemerin can affect the electrophysiology of the heart including myocytes in the sinoatrial node through sympathetic nervous system activation and ion channels, such as sodium, calcium by shortening the duration of action potentials.

It was foreseen with this study for the first time in the literature that chemerin, which was elevated in circulation of the patients with SVT, might contribute to the physiopathology of SVT, or might be used as a predictor. A positive correlation was detected between the elevated heart rate and plasma chemerin level in patients with SVT. Our study is original in this context in terms of its contribution to the literature.

The NLR, PLR, and CRP level, which were the independent predictors of SVT, and possible effect of chemerin on these values constituted another point that was investigated in our study. The number of the leukocyte subtypes and the NLR were among systemic inflammation indicators (31,32), and the important role of NLR in inflammation was discussed in previous studies conducted on SVT (33,34). CRP, which is one of the other markers of inflammation, is an important descriptive marker in patients with atrial tachycardia. Although the causal relation between CRP and atrial tachycardias is not fully elucidated, it can be concluded that inflammation will be associated with atrial tachycardias (4). Premature atrial and ventricular contractions are the most common triggering factors for SVTs. There is a strong relation between premature ventricular contractions and NLR. Other myocardial conditions and this inflammatory condition, which results in early contractions, have also roles in initiating SVTs (35-37). Based on these data, it can be speculated that the NLR, which will indicate a possible inflammatory condition, can also induce SVT (4). Also, the effects of anti-inflammatory axis of chemerin and its receptor CMKLR1 have also been reported in this respect. It is considered that chemerin inhibits neutrophil and monocyte aggregation in the peritonitis model, reduces proinflammatory mediators, and regulates the inflammatory process during which the presence of neutrophils may increase plasma chemerin levels by inducing the formation of chemerin homologues (38).

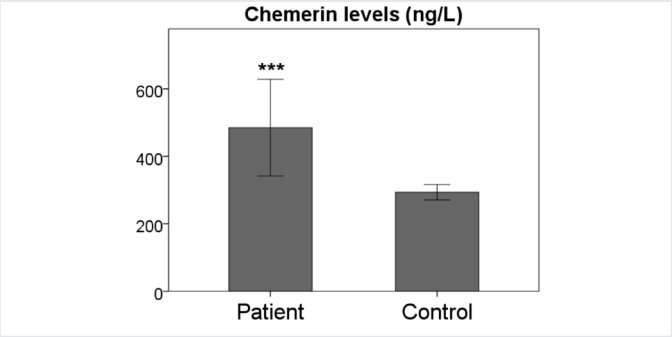


**Figure 1.** Difference in chemerin levels between the patient (SVT) group and control group (***p<0.001)

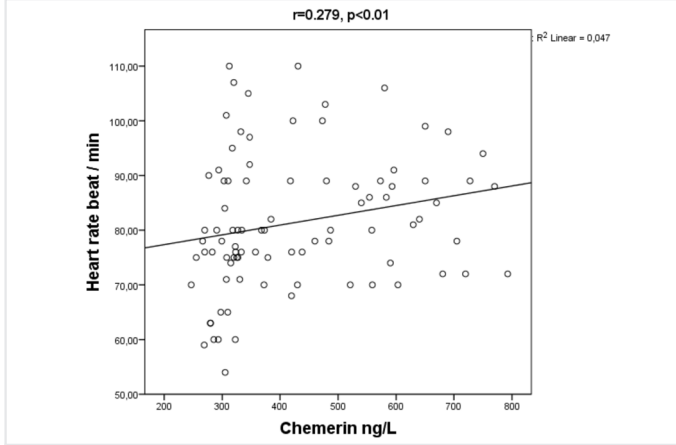


**Figure 2.** Correlation between chemerin and heart rate in the entire study group

**Table 2.** Independent predictors of supraventricular tachycardia

| Variable | Patient | | Control | | |
|---|---|---|---|---|---|
| | Median | SD | Median | SD | P |
| *NLR | 1.95 | 26.53 | 1.42 | 0.7 | **0.01** |
| *PLR | 122.09 | 1007.96 | 107.09 | 30.49 | 0.1 |
| *C-reactive protein | 0.45 | 1.23 | 0.3 | 1.34 | 0.27 |

NLR: Neutrophil/lymphocyte ratio, PLR: Platelet lymphocyte ratio, SD: Standard deviation

**Study Limitations**

The date of this study coincided with the coronavirus disease-19 pandemic, making it difficult to reach the number of patients required for the study. This study also demonstrated for the first time that there might be an association between SVT and chemerin, an endogenous adipocytokine. However, a cause-effect relationship could not be established in the relationship between chemerin and SVT, and a causality assessment could not be made.

## Conclusion

In conclusion, for the first time, the present study showed the relation between plasma chemerin level and SVT, and the positive relation between high chemerin concentration and heart rate was also revealed. Also, similar to previous studies, higher NLR, which was a reliable marker in inflammation, was associated with the presence of SVT. On the other hand, multicenter and wider-scale studies are required regarding the relations between inflammation, chemerin, and SVT trio in the pathogenesis process, which may be triggered by chemerin through ion gates, contributing to the organization of inflammation, which, then, may play roles in the formation mechanism of SVT, and this inflammatory process in the body.

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**Ethics**

**Ethics Committee Approval:** All procedures were performed after the study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (2019/350).

**Informed Consent:** Obtained.

**Peer-review:** Externally peer reviewed.

**Authorship Contributions**

Surgical and Medical Practices: Z.Y., Concept: Ö.K., Design: Ö.K., Data Collection or Processing: Ö.K., Z.Y., Analysis or Interpretation: Ö.K., Z.Y., Literature Search: Ö.K., Writing: Ö.K.

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

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# Hyperinflammatory Syndrome in Patients with COVID-19

## COVID-19 Hastalarında Hiperenflamatuvar Sendrom

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## ABSTRACT

**Objective:** The aim of this study was to investigate the relationship between the initial hyperinflammatory syndrome (HIS) risk score, calculated according to the clinical criteria recommended in the literature, and clinical outcomes in hospitalized patients with the diagnosis of coronavirus disease 2019-(COVID-19).

**Methods:** A total of 169 patients (93 females, 76 males, mean age: 65.10±14.74 years) who were hospitalized with a polymerase chain reaction-confirmed COVID-19 diagnosis at the time of hospitalization were consecutively enrolled in this retrospective, observational and clinical study. Those with two or more of the characteristics of fever, macrophage activation, haematological dysfunction, hepatic injury, coagulopathy, and cytokinemia constituted the group with high risk of HIS, and those with <2 constituted the group with low risk of HIS. Groups were compared according to their clinical characteristics and outcomes.

**Results:** There were 109 (64.5%) patients with a baseline HIS score of ≥2, and 60 (35.5%) patients with a baseline HIS score of <2. Mean length of stay (15.25±9.61 vs. 9.53±5.39, p<0.01), intensive care unit (ICU) admission (38.2% vs. 1.7%, p<0.01) mechanical ventilation need (MVN) (31.2% vs.1.7%, p<0.01) and mortality (24.8% vs. 0%, p<0.01) were higher in the HIS score ≥2 group than the HIS score <2 group. HIS score ≥2 increased the risk of ICU admission [odds ratio (OR) =36.5; 95% confidence interval (CI) =4.862], and the risk of MVN (OR =26.747; 95% CI =3.557)

**Conclusion:** The HIS score ≥2 at the time of hospitalization was associated with the increased risk of ICU admission, MVN and mortality. Initial HIS risk assessment in patients with COVID-19

## ÖZ

**Amaç:** Bu çalışmanın amacı koronavirüs hastalığı-2019 (COVID-19) tanısıyla hastaneye yatan hastalarda literatürde önerilen klinik kriterlere göre hesaplanan başlangıç hiperenflamatuvar sendrom (HİS) risk skoru ile klinik sonlanımlar arasındaki ilişkinin araştırılmasıydı.

**Yöntemler:** Bu retrospektif, gözlemsel ve klinik çalışmaya yatışında polimeraz zincir reaksiyonu ile COVID-19 tanısı konfirme edilen toplam 169 hasta (93 kadın, 76 erkek, ortalama yaş: 65,10±14,74 yıl) ardışık olarak alındı. Yatış esnasında yüksek ateş, makrofaj aktivasyonu, hematolojik disfonksiyon, hepatik enflamasyon, ve sitokinemi gibi 6 klinik özellikten 2 veya daha fazlasını bulunduran hastalar HİS gelişme riski yüksek grubu, <2 olanlar ise HİS gelişme riski düşük grubu oluşturdu. Gruplar klinik özelliklerine ve yoğun bakım ünitesine (YBÜ) yatış, mekanik ventilasyon ihtiyacı (MVİ) ve mortalite gibi klinik sonlanımlarına göre karşılaştırıldı. Olguların başlangıç risk skorlarının klinik sonlanımlar üzerinde ne kadar risk artışına neden olduklarını belirlemek için olasılık oranı hesaplandı.

**Bulgular:** Başlangıç HİS skoru ≥2 olan 109 (%64,5), <2 olan 60 (%35,5) olgu vardı. Tüm olgularda mortalite, YBÜ'ye yatış ve MVİ sıklıkları sırasıyla %16, %27,7 ve %20,7 idi. HİS skoru ≥2 olan grupta ortalama yatış süresi (15,25±9,61'e karşılık 9,53±5,39, p<0,01), YBÜ'ye yatış (%38,2'ye karşılık %1,7, p<0,01), MVİ (%31,2'ye karşılık %1,7, p<0,01) ve mortalite (%24,8'e karşılık %0, p<0,01) sıklıkları HİS skoru <2 olan gruba göre yüksekti. HİS skoru ≥2 olmasının YBÜ yatış riskini 36,5 kat [olasılık oranı (OO) =36,524; %95 güven aralığı (GA) =4,862-274,351], MVİ riskini 26,7 kat (OO =26,747; %95 GA =3,557-201,145) artırdığı görüldü.

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**ABSTRACT**

could be useful to predict the prognosis and to select patients for immunomodulatory therapy.

**Keywords:** COVID-19, hyperinflammatory syndrome, risk score, immunomodulatory therapy, prognosis

**ÖZ**

Başlangıç HİS skoru yüksek olanlarda HİS skorunu oluşturan klinik özellikler içerisinde yüksek ateş, hematolojik disfonksiyon ve sitokinemi varlığının YBÜ'ye yatış, MVİ ve mortalite riskini anlamlı artırdığı görüldü.

**Sonuç:** Bu çalışmanın sonuçları, COVID-19 nedeniyle hastaneye yatan hastalarda yatış anında HİS skorunun yüksek bulunmasının YBÜ'ye yatış, MVİ ve mortalite riskindeki artış ile ilişkili olduğunu göstermiştir. Bu bulgular, COVID-19'lu hastalarda HİS risk değerlendirmesinin hem prognozu öngörmede hem de immünomodülatör tedavi için hasta seçiminde yararlı bir araç olarak kullanılabileceği bilgisini desteklemiştir.

**Anahtar Sözcükler:** COVID-19, hiperenflamatuvar sendrom, risk skor, immünodülatör tedavi, prognoz

## Introduction

The patients hospitalized with coronavirus disease-2019 (COVID-19) develop hyperinflammatory complications of severe COVID-19 infection or cytokine storm syndrome, which is frequently fatal (1,2). It seems that uncontrolled macrophage and monocyte activation due to impaired interferon response in COVID-19 immunopathology has a key role in hyperinflammatory response and organ injury and also genetic polymorphism associated with hyperinflammatory response may have a partial role (3-7). It was reported that the early usage of immunomodulatory therapies such as corticosteroids, cell-signalling inhibitors and anti-cytokine antibodies were vital in attenuating the early inflammatory response in order to prevent organ failure associated with hyperinflammation in COVID-19 (8-16). Although there were many studies that clearly showed the relationship between disease severity and immuno-inflammatory parameters in COVID-19, it was controversial how to define the COVID-19-associated hyperinflammatory syndrome (HIS) and which criteria could be useful for it (17-23). Webb et al. (24) developed a scoring system that could predict the probability of development of HIS in patients with COVID-19 by taking advantage of the features seen in other hyperinflammatory and cytokine storm syndromes such as secondary hemophagocytic lymphohistiocytosis, macrophage activation syndrome and cytokine release syndrome. According to this system, it was reported that the presence of 2 or more of the 6 physiological features such as fever, macrophage activation, hematological dysfunction, hepatic inflammation, coagulopathy and cytokinemia could be used for demonstrating in-hospital mortality and the need for mechanical ventilation.

In this study, we aimed to evaluate the relationship between the initial HIS risk score and the clinical outcomes of hospitalization in the intensive care unit (ICU), mechanical ventilation need (MVN) and mortality in patients hospitalized with the diagnosis of COVID-19.

## Methods

Patients hospitalized in İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital between 01.12.2020 and 31.01.2021 with a diagnosis of polymerase chain reaction (PCR)-confirmed COVID-19 were consecutively included in the single-center, retrospective, observational and clinical study. The study was approved by the local ethics committee (date and number: 27.01.2021-2021/0070) and the principles of the Declaration of Helsinki were followed throughout the study.

Inclusion criteria: Being ≥18 years old, diagnosed as having COVID-19 confirmed by real-time PCR, chest X-ray and/or chest computed tomography (CT) findings compatible with the diagnosis of COVID-19.

### Exclusion Criteria

Lack of clinical or laboratory data, patients already hospitalized in the ICU;

**Primary endpoint:** Investigation of the relationship between the initial HIS risk score calculated according to the clinical criteria recommended in the literature and the clinical outcomes of hospitalization in the ICU, MVN, and mortality in patients hospitalized with the diagnosis of COVID-19.

### Study Design

Demographic characteristics, physical examination findings, comorbidities, treatment characteristics, laboratory and imaging data (complete blood count, fasting glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, electrolytes, lactate dehydrogenase (LDH), ferritin, C-reactive protein, troponin I, D-dimer, interleukin-6, lipids, chest CT), length of stay, clinical outcomes (ICU admission, MVN development, and mortality) of the patients included in the study were recorded. The scoring system recommended by Webb et al. (24) was used to evaluate the risk of developing HIS during hospitalization. According to this system, patients with 2 or more of 6 clinical features such as fever (>38 °C), macrophage activation (ferritin ≥700 μg/L), hematological dysfunction (neutrophil-lymphocyte ratio ≥10 or hemoglobin ≤9.2 g/dL or platelet ≤110x$10^9$ cells/L), hepatic inflammation (LDH ≥400 U/L or AST ≥100 U/L), coagulopathy (D-dimer ≥1.5 μg/mL) and cytokinemia (C-reactive protein ≥15 mg/dL or interleukin-6

≥15 pg/mL or triglyceride ≥150 mg/dL) during hospitalization were categorized in the group with a high risk of HIS and those with <2 in the group with a low risk of HIS and groups were compared according to their demographic characteristics, comorbidities, length of stay, clinical outcomes, and laboratory characteristics. The odds ratio (OR) was calculated to determine how much the initial risk scores of the patients caused an increased risk on clinical outcomes.

**Statistical Analysis**

The IBM SPSS Statistics 22.0 program was used for statistical analysis. While evaluating the study data, the compatibility of the parameters with the normal distribution was evaluated with the Kolmogorov-Smirnov test. In addition to descriptive statistical methods (mean, Standard deviation), Student's t-test was used for the comparison of normally distributed quantitative data between two groups, and Mann-Whitney U test was used for comparisons of non-normally distributed parameters between two groups. Chi-square test, Fisher's Exact test and Continuity Correction (Yates) test were used to compare qualitative data. Significance was evaluated at the $p<0.05$ level.

## Results

A total of 169 patients (93 women 55%, 76 men 45%, mean age: 65.10±14.74 years, mean length of stay: 13.2±8.7 days) were included in the study.

Of all patients, 40 (23.7%) required ICU admission, 35 (20.7%) required MVN, and mortality was observed in 27 (16%). There were 109 (64.5%) patients with a baseline HIS score of ≥2, and 60 (35.5%) patients with a baseline HIS score of <2. There were 18 (10.7%) patients with a HIS score of 0.42 (24.9%) with 1.43 (25.4%) with 2.35 (20.7%) with 3, 18 (10.7%) with 4, 10 (5.9%) with 5 and 3 (1.8%) with 6.

The clinical and laboratory characteristics of groups were given in Table 1. In the group with HIS score ≥2, mean length of stay (15.25±9.61 vs. 9.53±5.39, $p<0.01$), ICU admission (35.8% vs. 1.7%, $p<0.01$), MVN (31.2% vs. 1.7%, $p<0.01$) and the mortality (24.8% vs. 0%, $p<0.01$) were higher than the group with HIS score <2. It was observed that a HIS score of ≥2 increased the risk of hospitalization in ICU 36.524 times [OR =36,524; 95% confidence interval (CI) =4,862-274,351], and MVN 26,747 times (OR =26,747; 95%, CI =3,557-201,145). In those with HIS score ≥2 compared to those with HIS score <2, white blood cell count ($p=0.001$), neutrophil to lymphocyte ratio ($p=0.001$), ferritin level ($p=0.001$), C-reactive protein level ($p=0.001$), creatinine level ($p=0.037$), AST level ($p=0.001$), ALT level ($p=0.047$), LDH level ($p=0.001$), D-dimer level ($p=0.001$), troponin level ($p=0.008$) and interleukin-6 ($p=0.001$) level were found to be higher and absolute lymphocyte count ($p=0.009$) was found to be lower.

The distribution of the six clinical features used to determine the risk of developing HIS according to the groups were given in Table 2. In the group with HIS score ≥2, frequencies of fever (>38 ºC), macrophage activation (ferritin ≥700 µg/L), hematological dysfunction (neutrophil-lymphocyte ratio ≥10 and platelet ≤110x$10^9$ cells/L), hepatic inflammation (LDH ≥400 U/L), coagulopathy (D-dimer ≥1.5 µg/mL), and cytokinemia (C-reactive protein ≥15 mg/dL or interleukin-6 ≥15 pg/mL) were higher than the group with HIS score <2 (for all $p<0.01$).

In all patients, high fever (OR =10.071; 95%, CI =4.388-23.116), hematological dysfunction (OR =4.727; 95% CI =2.126-10.510), hepatic injury (OR =3.805; 95%, CI =1.806-8.019) and cytokinemia (OR =3.430; 95%, CI =1.337-8.797) significantly increased the risk of ICU admission; fever (OR=10,889; 95%, CI= 4.374-27.108), hematological dysfunction (OR =5.082; 95%, CI =2.260-11.425), and cytokinemia (OR =3.459; 95%, CI =1.260-9.496) significantly increased the risk of MVN; and fever (OR =6.467; 95%, CI =2.681-15.602), hematological dysfunction (OR =6.467; 95%, CI =2.681-15.602), and cytokinemia (OR =7.222; 95%, CI =1.644-31.733) significantly increased the risk of mortality.

## Discussion

The HIS is one of the most important causes of mortality in patients hospitalized due to COVID-19, and predicting which patients may develop HIS during hospitalization can be a guide for clinicians, especially for the early initiation of immune-modulatory treatments. However, studies are continuing on which parameters can adequately predict the risk of HIS. Caricchio et al. (25) stated that the criteria specified for macrophage activation syndrome, hemophagocytic lymphohistiocytosis and HIS score could not define the COVID-19 cytokine storm. However, they also showed the fact that increased C-reactive protein and ferritin levels were associated with at least one variable in each of the three laboratory clusters, including systemic inflammation (low albumin, lymphopenia, neutrophilia), cell death and tissue damage (AST, ALT, LDH, D-dimer and troponin-I). Also prerenal electrolyte imbalance (chloride, potassium, sodium, BUN and creatinine) can adequately predict long hospital stay and increased mortality associated with hyperinflammation and tissue damage in the COVID-19 cytokine storm (25). In an analysis, Webb et al. (24) compared the clinical features of patients with secondary haemophagocytic lymphohistiocytosis, macrophage activation syndrome, macrophage activation-like syndrome of sepsis, and cytokine release syndrome with the data of patients with COVID-19, and they developed a risk scale for COVID-19-related HIS using these features. They reported that the presence of two or more of the six physiological characteristic categories including fever, macrophage activation (hyperferritinemia), haematological dysfunction (neutrophil to lymphocyte ratio), hepatic injury (LDH or AST), coagulopathy (D-dimer), and cytokinemia (C-reactive protein, interleukin-6, or triglycerides) during hospitalization in patients with the diagnosis of COVID-19 could be used as a useful tool showing increased hospital mortality and the need for mechanical ventilation. In that study, it was observed that mortality and MVN were higher in those with a baseline HIS score of ≥2 than in those with a HIS score of <2 (15% vs. 1% and 45% vs. 2%, respectively). It was also reported that unadjusted discrimination

of maximal daily HIS score (unadjusted discrimination) was 0.81 for in-hospital mortality, 0.92 for mechanical ventilation, and remained significant in multivariate analysis (OR 1.6 for mortality, OR 4.3 for mechanical ventilation).

In our study it was observed that the mean length of stay was longer, and mortality, ICU need and MVN, and the levels of all laboratory parameters including the HIS score, except triglyceride, were found to be significantly higher in patients with high initial HIS score (≥2) than those with low initial HIS score (<2). It was observed that no mortality developed in those with a low initial HIS score, and a high initial HIS score increased the risk of hospitalization in ICU 36.5 times and the risk of MVI 26.7 times. On the other hand, it was observed that among the clinical features composing the HIS score, especially the presence

**Table 1.** Clinical and laboratory characteristics of patients with COVID-19

| | HIS score <2 (n=60) | HIS score ≥2 (n=109) | *p value |
|---|---|---|---|
| Age (mean ± SD) | 64.1±15.9 | 65.6±14.0 | 0.521 |
| **Sex (n,%)** | | | |
| Female<br>Male | 29 (48.3)<br>31 (51.7) | 64 (58.7)<br>45 (41.3) | 0.194 |
| **Outcomes** | | | |
| Length of hospital stay (mean ± SD) | 9.53±5.39 | 15.25±9.61 | **0.001** |
| ICU (n,%) | 1 (1.7) | 39 (35.8) | **0.001** |
| MCN (n,%) | 1 (1.7) | 34 (31.2) | **0.001** |
| Mortality rate (n,%) | 0 (0) | 27 (24.8) | **0.001** |
| **Comorbidities (n,%)** | | | |
| Diabetes | 19 (31.7) | 42(38.5) | 0.470 |
| Hypertension | 27 (45) | 58 (53.2) | 0.307 |
| Coronary artery disease | 16 (26.7) | 27 (24.8) | 0.931 |
| Chronic kidney disease | 5 (8.3) | 7 (6.4) | 0.756 |
| Congestive heart failure | 3 (5) | 9 (8.3) | 0.542 |
| Chronic pulmonary disease | 3 (5) | 8 (7.3) | 0.748 |
| Active malignancy | 2 (3.3) | 12 (11) | 0.142 |
| Cerebrovascular disease | 4 (6.7) | 4 (3.7) | 0.456 |
| HGB, (g/dL) | 13.08±1.68 | 12.68±1.91 | 0.173 |
| PLT, $10^9$ cells per L | 201.2±60.45 | 189.68±85.03 | 0.355 |
| WBC, $10^9$ cells per L | 5635±2174.73 | 7734.4±4030.52 | **0.001** |
| LYM, $10^9$ cells per L | 1218.33±541.96 | 1060.73±741.89 | **0.009** |
| NLR | 3.97±2.91 | 7.99±10.14 | **0.001** |
| Ferritin (ng/mL) | 225.28±188.71 | 1227.24±2086.44 | **0.001** |
| CRP, mg/dL | 4.91±4.04 | 10.77±7.94 | **0.001** |
| Glucose (mg/dL) | 122.82±46.13 | 138.87±58.82 | 0.097 |
| Creatinine, mg/dL | 0.99±0.44 | 1.36±1.59 | **0.037** |
| AST, U/L | 31.75±13.12 | 44.96±25.93 | **0.001** |
| ALT, U/L | 28.87±21.23 | 39.29±39.94 | **0.047** |
| LDH, U/L | 278.64±95.65 | 429.17±193.78 | **0.001** |
| D-dimer, µg/mL | 1.16±2.7 | 2.04±3.21 | **0.001** |
| Troponin | 18.91±26.28 | 101.75±582.19 | **0.008** |
| INR | 1.26±0.7 | 1.72±3.29 | 0.346 |
| IL-6, pg/mL | 19.28±18.88 | 95.8±392.97 | **0.001** |
| TG, mg/dL | 113.56±51.86 | 124.13±61.11 | 0.372 |

*p value <0.05 ICU: Intensive care unite., MCN: Mechanical ventilation need, HGB: Haemoglobin, PLT: Platelet count, WBC: White blood cell count, LYM: Absolute lymphocyte count, CRP: C-reactive protein, AST; Aspartate aminotransferase, LDH: Lactate dehydrogenase, NLR: Neutrophil to lymphocyte ratio, INR: Internationalized normalized ratio, IL-6: Interleukin-6 , TG: Triglyceride, SD: Standard deviation

**Table 2.** The distribution of the clinical features used to determine the risk of developing HIS according to the groups

| | HIS score <2 (n=60) (n;%) | HIS score ≥2 (n=109) (n;%) | *p value |
|---|---|---|---|
| Fever (>38 ˚C) | 10 (16.7) | 54 (49.5) | **0.001** |
| Hgb ≤9.2 g/dL | 8 (7.3) | 9 (5.3) | 0.161 |
| PLT ≤110 cells per L | 0 (0) | 14 (2.8) | **0.002** |
| NLR ≥10 | 1 (1.7) | 23 (21.1) | **0.001** |
| Ferritin ≥700 ng/mL | 1 (1.7) | 52 (48.1) | **0.001** |
| CRP ≥15 mg/dL | 0 (0) | 24 (22.2) | **0.001** |
| AST ≥100 U/L | 0 (0) | 3 (2.8) | 0.553 |
| LDH ≥400 U/L | 3 (5.5) | 52 (50) | **0.001** |
| D-dimer ≥1.5 µg/mL | 6 (10.3) | 41 (37.6) | **0.001** |
| IL-6 ≥15 pg/mL | 21 (42.9) | 81 (86.2) | **0.001** |
| TG ≥150 mg/dL | 8 (18.6) | 22 (25.6) | 0.507 |

*P value <0.05 AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, NLR: Neutrophil to lymphocyte ratio, IL-6: Interleukin-6, CRP: C-reactive protein, PLT: Platelet count, Hgb: Haemoglobin, TG: Triglyceride

of high fever, hematological dysfunction and cytokinemia significantly increased the risk of ICU admission, MVN, and mortality in patients with a high initial HIS score.

It is known that demographic characteristics such as advanced age, male gender and comorbid conditions such as diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, heart failure and malignancy are associated with an increase in disease severity and mortality in patients with COVID-19 (26,27). In our study, age, gender and distribution of comorbid conditions did not different significantly between those with and without a high initial HIS score. Although hypertension found in approximately one out of every two persons, diabetes mellitus in one out of three persons, and concomitant coronary artery disease in one out of every four persons support the knowledge that comorbid conditions frequently accompany COVID-19 infection, the results of our study suggest that comorbid conditions do not cause a significant increase in the risk of developing HIS.

### Study Limitations

The study's limitations include the retrospective nature of the assessment and the relatively low number of patients.

## Conclusion

The presented study showed that HIS score calculated at the time of hospitalization of the patients with COVID-19 was associated with increased risk of ICU admission, MVN, mortality and HIS risk score assessment in patients with COVID-19 could be useful for both in predicting prognosis and patient selection for immunomodulatory therapy. On the other hand, it should be considered that the risk of developing HIS and poor clinical outcome might be high in patients with COVID-19 who have high fever, hematological dysfunction and cytokinemia during hospitalization.

### Ethics

**Ethics Committee Approval:** The study was approved by the local ethics committee (date and number: 27.01.2021-2021/0070) and the principles of the Declaration of Helsinki were followed throughout the study.

**Informed Consent:** The single-center, retrospective, observational and clinical study.

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.U., H.Ş.M., E.E., Concept: M.U., H.V., Design: M.U., Ş.M., Data Collection or Processing: Ş.M., E.E., O.İ., Analysis or Interpretation: M.U., Ş.M., E.E., H.V., Literature Search: M.U., Ş.M., E.E., O.İ., H.V., Writing: M.U., E.E.

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

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Original Article

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# Effect of Translucency on Color Stability of Resin-based Composites

## Yarı Saydamlığın Rezin Bazlı Kompozitlerin Renk Stabilitesi Üzerindeki Etkisi

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### ABSTRACT

**Objective:** This study evaluated the effect of translucency on the color stability of resin-based composites (RBCs).

**Methods:** Different translucent/opaque shades of RBCs were used: Filtek Ultimate (FU); A2 Enamel, A2 Dentin, A2 Body, IPS Empres Direct (IED); A2 Enamel, A2 Dentin, GC Essentia (GC); LE, MD, Estelite Σ Quick (EQ); OA2, A2, CeramX duoSphertec and One (CX); E2, D2, A2. Disc-shaped specimens were stained in coffe and then brushed. The color changes (ΔE) were calculated between baseline and treatment. One-way ANOVA and Tukey's post-hoc test were used for statistical analysis (α=0.05).

**Results:** After staining, the difference between the ΔE values of RBCs was not statistically significant, except GC LE. After both staining and brushing, the ΔE values of the enamel shades were the highest, and the order of ΔE values was body > dentin for ESQ and CX, dentin > body for FU.

**Conclusion:** The ΔE values of the enamel shades were the highest after both staining and brushing.

**Keywords:** Composite resin, color stability, translucency, whitening toothpaste, toothbrush

### ÖZ

**Amaç:** Bu çalışmada, yarı saydamlığın rezin bazlı kompozitlerin (RBC) renk stabilitesi üzerindeki etkisi değerlendirildi.

**Yöntemler:** RBC'lerin farklı yarı saydam/opak tonları kullanıldı: Filtek Ultimate (FU); A2 Mine, A2 Dentin, A2 Body, IPS Empres Direct (IED); A2 Mine, A2 Dentin, GC Essentia (GC); LE, MD, Estelite Σ Hızlı (EQ); OA2, A2, CeramX duoSphertec ve One (CX); E2, D2, A2. Disk şeklindeki numuneler kahve ile renklendirildi ve daha sonra fırçalandı. Renk değişiklikleri (AE), başlangıç ve tedavi sonrası olarak hesaplandı. İstatistiksel analiz için one-way ANOVA ve Tukey post-hoc testleri kullanıldı(α=0,05).

**Bulgular:** Renklenmeden sonra, RBC'lerin ΔE değerleri arasındaki fark, GC LE dışında istatistiksel olarak anlamlı bulunmadı. Hem renklendirme hem de fırçalama sonrasında en yüksek ΔE değerleri mine renklerinde görüldü ve ΔE değerlerinin sırası ESQ ve CX için body > dentin, FU için ise dentin > body şeklinde bulundu.

**Sonuç:** En yüksek ΔE değerleri hem renklenme hem de fırçalama sonrasında mine renklerinde görüldü.

**Anahtar Sözcükler:** Kompozit rezin, renk stabilitesi, yarı saydamlık, beyazlatıcı diş macunu, diş fırçası

## Introduction

The general aesthetic understanding prefers natural looking aesthetics as much as possible (1). To achieve ultimate aesthetics, restorations should mimic not only the color of the natural tooth but also the translucency. Its translucency provides a "lifelike" vitality and a natural appearance to the completed restoration (2). For this reason, composite resin manufacturers produce resins with

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different colors and different translucency/opaque shade options. In some cases, it is sufficient to use only a universal composite resin to create a natural looking restoration. However, in some cases, more opaque composite resins are required to mask the composite resin-tooth interface, hide the dark background of the oral cavity, cover tooth tissue that appears darker than normal, and recreate the high value needed in the center of the tooth (3). Although these opaque composite resins (dentin) sometimes remain on the buccal surfaces of restorations, they are often coated with translucent (enamel) because of the terminology "dentin" and "enamel" used for different pastes of resin-based composites. In addition, translucent resins are used to enrich the optical properties of the incisal area of the tooth.

In addition to accurately imitating the optical properties of natural teeth with restorative materials, the color stability of these restorations is also very important for clinical success (4). Some intrinsic and extrinsic factors affect color stability in resin-based composites. Chemical changes within the material, such as oxidation of unreacted monomers and photoinitiator components that are not consumed during photopolymerization (5), hydrolysis of silane between filler particles and polymer matrix (6), are the causes of intrinsic discoloration. Diffusion of ions and pigments that can accumulate on the composite resin causes extrinsic discoloration (7). Diet and oral hygiene habits significantly affect the color stability of composite resins (8,9). The translucency property of composite resins depends on many factors affecting the chemical composition of the composites, such as filler content, particle composition, monomer properties, and minor pigment additions (10,11). These factors can also affect their coloration stability. On the other hand, it is speculated that the highly translucent character may compromise the optical stability, since pigments and oxidized unreacted species may become more apparent in the bulk of the restoration (12). There are many studies in the literature investigating the color stability of composites. However, there are very few studies evaluating the effects of translucency in composites on color stability (3,12).

The aim of this study was to determine the color stability of five different trademark resin-based composite systems in the different available translucent/opaque shades. The hypotheses of this study were that:

1. There is no difference between the color stability of resin based composites subjected to coffee solution.

2. There is no effect of translucency within each brand on color stability.

3. There is no difference between the color stability of the resin based composites subjected to tooth-brushing simulation.

## Methods

In this study, five commercially-available resin based composites indicated for aesthetic restorations were selected in different translucent/opaque shades: Filtek Ultimate (FU); A2 Enamel, A2 Dentin, A2 Body, IPS Empres Direct (IED); A2 Enamel, A2 Dentin, GC Essentia (GC); LE (Enamel), MD (Dentin), Estelite Σ Quick (EQ); OA2 (Dentin), A2 (Body), Ceram X duo Sphertec (CX); E2 (Enamel), D2 (Dentin), Ceram X One (CX); A2 (Body). The compositions and manufacturers of the resin based composites used are included in Table 1.

Fourteen disc-shaped specimens were made for each composite resin using a cylindrical polytetrafluoroethylene (teflon) mold of 8-mm inner diameter and 2-mm thickness. After composite insertion, top surface was covered with a Mylar strip and made flat by pressing down with a glass slab. The specimens were light activated for 30 s from the top surface using a large spectrum (385-515 nm) light emitting diode curing unit (Blue lex LD-105, Monitex Industrial Co, Taiwan) with irradiance of 1,200 mW/cm$^2$. The samples were stored in dry/dark condition for 24 h. Then, they were polished with OneGloss (Shofu) polishing rubbers containing aluminum oxide particles that provided finishing and polishing by changing the application pressure only in one step.

Then the samples were randomly divided into two groups as staining and non-staining (n=7). The samples in the non-staining group were kept in water for 3 weeks. The samples in the staining group, after 1 week water storage, immersed in coffee solution (Nescafe Gold Nestl´e, Suisse S.A. Switzerland, Batch-01740202A) for 45 minutes a day and in water at other times for 2 weeks (13,14). Coffee solution was preferred as it was one of the most consumed beverages worldwide as a coloring solution. The coffee manufacturer states that the average time for consumption of one cup of a drink is 15 min, and, among coffee drinkers, the average consumption of coffee is 3.2 cups per day. Thus approximately 14 days of coloration was simulated. The coffee solution was obtained by adding a spoonful of soluble coffee to 250 mL of boiled water, followed by stirring and cooling to room temperature. The solution was then inserted in 96- well eppendorf plates with the specimens and daily prepared.

The samples in the staining group, after staining with coffee solution for 2 weeks , were brushed with an electrical toothbrush (Oral-B Professional, Braun, Frankfurt, Germany) fixed on a holder and with a whitening toothpaste (Colgate Optic White, Colgate-Palmolive, Poland) with a paste-to-water ratio of 1:1 for 45 second. The content of the toothpaste used in the study is shown in Table 1. The average brushing time was assumed to be 120 seconds twice a day, which equated to approximately 3 seconds of brushing a tooth surface per day. According to this calculation, brushing for 45 seconds could be equal to approximately 2 weeks of brushing as in our staining period.

The color of specimens was measured with a VITA Easyshade V (VITA Zahnfabrik, Bad Säckingen,Germany) spectrophotometer, calibrated before starting and after the measurement of every 10 samples. The diameter of the measuring tip was 6 mm. Composite discs were placed on a flat White surface. The spectrophotometer tip was always placed perpendicularly to the disc surface (7). Measurements were made from the center of the samples each time, with the measuring tip of the device right in the middle. Color measurement of the all samples was made at baseline (after 24 h of specimen's curing and dry/dark

storage). Then, it was made after 3 weeks of immersion in water in the non-staining group, and it was made at the end of the coloring period with coffee and after brushing it was repeated in the staining group. Before the color was measured, the specimens were washed in water for 1 min and dried with tissue paper. The color measurement of each specimen was repeated three times by a single operator, and the mean of the three readings was taken. The variation in color was established based on the coordinates: L (lightness, 0-100), a (-a* = green, +a* = red) and b (-b* = blue, +b* = yellow) of the CIEL*a*b* scale. The color changes of the samples were evaluated with the ΔE * parameter calculated using L, a and b values. The ΔE * value is the color change that an observer can detect after the application and in time intervals. This value alone is more significant than L, a, b values.

$\Delta E^* = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$

$\Delta L^* = L2-L1$

$\Delta a^* = a2-a1$

$\Delta b^* = b2-b1$

ΔE were calculated between baseline and after the treatments.

**Statistical Analysis**

The SPSS 15.0 package program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the data. First of all, whether the data showed normal distribution and the homogeneity of the variances were checked. Since the data showed normal distribution and the variances were homogeneous, the one-way analysis of variance (One-Way ANOVA), a parametric test method, was used for the statistical evaluation of the color change (ΔE) data of the samples. Tukey HSD test was used to compare the differences between groups.

## Results

The standard deviations and mean of ΔE values are shown in Table 2 and Figure 1.

**Table 1.** Composition of the commercially available resin-based composites and toothpaste used in this study

| Material | Components | Filler content % (w/w) | Manufacturer |
|---|---|---|---|
| Essentia | Matrix: UDMA, Bis-MEPP, Bis-EMA, Bis-GMA, TEGDMA<br>Filler: prepolymerised fillers, barium glass, fumed silica | 81 | GC Corporation, Tokyo, Japan |
| IPS empress direct | Matrix: UDMA, Bis-GMA, TEGDMA<br>Filler: Barium glass, ytterbium trifluoride, and mixed oxides (0.5 μm) | 81.2 | Ivoclar Vivadent; Schaan, Liechtenstein |
| Tokuyama Estelite Σ Quick | Matrix: Bis-GMA, Bis-MPEPP, TEGDMA, UDMA<br>Filler: Supra-nano Spherical filler (200nm spherical SiO2-ZrO2), Composite Filler (include 200nm spherical SiO2-ZrO2). | 82 | Tokuyama Dental corporation, Taitou-ku Tokyo, Japan |
| Ceram.X one Universal | Matrix: methacrylate modified ploysiloxane, dimethacylate resin, ethyl4 (dymethylamino)benzoate<br>Filler: Barium-aluminium borosilicate glass (1.1-1.5 μm), Methacrylate functionalized silicon dioxide nano filler (10 nm) | 76 | Dentsply De Trey, Konstanz, Germany |
| Ceram X Duo Sphertec | Matrix:Methacrylate modified polysiloxane, dimethacrylate resin, ethyl4(dimethylamino)benzoate, Fillers: barium aluminium-borosilicate glass, methacrylate functionalized silicon dioxide nano filler, | 76 | Dentsply De Trey, Konstanz, Germany |
| Filtek Utimate | Matrix: Bis-GMA, UDMA, TEGDMA, bis-EMA and PEGDMA resins<br>Filler: Silica, zirconia and aggregated zirconia/silica cluster fillers, 0.6 – 10 μm in size | 78.5 | 3M ESPE, Seefeld, Germany |
| Colgate Optic White | Sodium monofluorophosphate (1300 ppm flüoride), propylene glycol, calcium pyrophosphate, glycerin, PEG/PPG-116/66 copolymer, PEG-12,PVP, silica, flavor, sodium lauryl sulfate, tetrasodium pyrophosphate, hydrogen peroxide, disodium pyrophosphate, sodium saccharin, sucralose, BHT | | Colgate, Palmolive, Poland |

UDMA: Urethane dimethacrylate, Bis-MEPP: Bisphenol a ethoxylate dımethacrylate, BIS-EMA: Ethoxylated bisphenol A glycol dimethacrylate, Bis-GMA: Bisphenol A diglycidyl methacrylate, TEGDMA: Triethylene glycol dimethacrylate, PEGDMA: Polyethylene glycol dimethacrylate

After storage in water, there was a color change between the baseline and post- immersion period for all composite resins. CX A2 resins showed the least color change and FU Dentin showed the most color change. Although the difference between these two resins was statistically significant, the differences between the other resins were not statistically significant.

Coffee staining caused statistically significantly more coloration for all resin-based composites compared to samples stored in water. GC Enamel stained more than all resins. The difference between the ΔE values of other composite resins except GC Enamel was not statistically significant.

After brushing, except CX dentin, the ΔE values for all composite resins were lower than the ΔE values after staining, but higher than the ΔE values of water storage group. ΔE values of GC enamel and IED enamel were statistically significantly higher than other resins.

When composite resins of the same brand were compared within themselves, the color change values of the enamel shades were the highest after both staining and brushing, for all commercial brands, except CX enamel after staining. The amount of color change of dentin and body shades differed according to the brands. Although the difference between them was not

**Table 2.** Resuts for color difference (ΔE) considering three periods: ΔE 1 (baseline and water storage) ΔE 2 (Baseline and coffee solution storage) and ΔE 3 (baseline and brushing). Values are given as means ± standard deviations (n=7). Different letters show statistically significant differences (p<0.05), uppercase letters indicate columns; lowercase letters point to lines

| **Estelite Σ quick** | ΔE 1 | ΔE 2 | ΔE 3 |
|---|---|---|---|
| A2 (body) | 1.84±0.79 Aabc | 8.73±3.66 Ba | 4.96±2.03 Cab |
| OA2 (dentin) | 1.26±0.27 Aabc | 7.53±1.39 Ba | 3.55±1.29 Ca |
| **Filtek ultimate** | | | |
| A2 (body) | 1.06±0.42 Aabc | 8.13±3.39 Ba | 2.82±1.30 Ca |
| A2 (dentin) | 2.21±0.86 Ab | 8.65±2.24 Ba | 4.29±1.01 Ca |
| A2 (enamel) | 2.03±1.19 Aabc | 10.30±2.27 Ba | 5.19±2.24 Cab |
| **IPS empres direct** | | | |
| A2D (dentin) | 1.40±0.41 Aabc | 8.53±2.02 Ba | 4.51±1.88 Cab |
| A2E (enamel) | 1.64±0.90 Aabc | 9.82±2.71 Ba | 7.51±2.49 Bbc |
| **Ceram X** | | | |
| D2 (dentin) | 1.54± 0.83 Aabc | 9.95±2.85 Ba | 3.30±1.58 Aa |
| E2 (enamel) | 1.22±0.56 Aabc | 9.15±2.10 Ba | 5.56±1.76 Cab |
| A2 (body) | 0.85±0.45 Ac | 11.13±3.32 Ba | 5.12±1.23 Cab |
| **GC essentia** | | | |
| MD (dentin) | 1.89±0.70 Aabc | 10.75±2.36 Ba | 4.75±1.34 Cab |
| LE (enamel) | 1.78±0.56 Aabc | 19.07±1.78 Bb | 9.86±2.09 Cc |

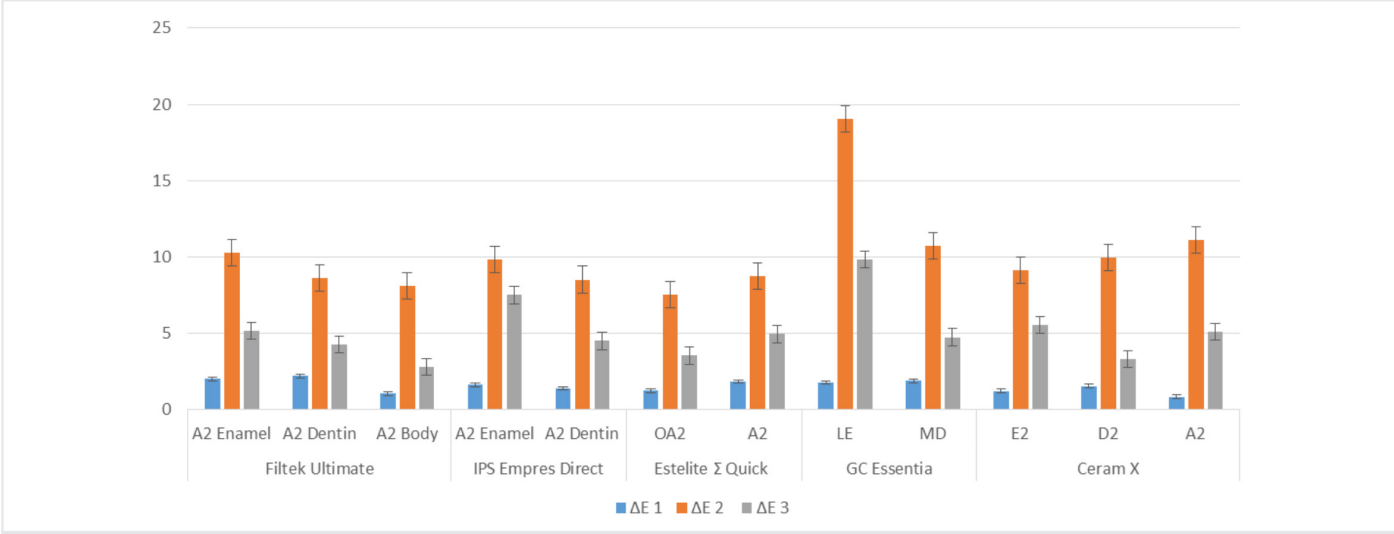


**Figure 1.** Results for color difference (&8710;E) considering three periods: &916;E 1 (baseline and water storage) &916;E 2 (Baseline and coffee solution storage) and &916;E 3 (baseline and brushing). Values are given as means ± standard deviations

statistically significant, the order of ΔE values in both staining and brushing groups was body > dentin for ESQ and CX and it is dentin > body for FU.

## Discussion

In the present study, the color stability of composite resins and the effect of translucency on the color stability were evaluated. For this purpose, resin-based composite systems of different brands and their different translucent/opaque shades were used.

In order to evaluate the color stability of composite resins, some samples were stored in water. Because the color change in composite resins with immersion in water was reported in previous studies (15-17). Similarly to these studies, there was a color change between the baseline and post- water immersion period in the present study.

There is no colorant in the water, but a color change occurs as a result of the absorption of water into the resin matrix (18). The refractive indexes of the polymer and water are different from each other, altering the light transmission after water accesses the polymer structure and leading to changes in color perception (19). On the other hand, it has been previously reported that in resin based composites, color change may occur as a result of oxidation of unreacted monomers held in the polymer network and photoinitiators that are not consumed during exposure to light (5). The release of these components causes color change when placed in an aqueous environment (5,20,21).

In the present study, after storage in water, CX A2 resins showed the least color change and FU Dentin showed the most color change. Although the difference between these two resins was statistically significant, the differences with the other resins were not statistically significant. Sideridou et al. (22) reported that the hydrophilicity of resin was in the following order: TEGDMA > Bis-GMA > UDMA and Bis-EMA. The reason CX A2 shows the least color change may be related to a low water absorption rate due to the absence of TEGDMA. In fact, both Ceram X sphertec one and duo do not contain TEGDMA. However, even small chemical differences such as pigment additions that can affect the translucency of dental resin-based composites can affect the stability of coloration (10,11).

Chen attributed the discoloration of nano-composites to their clusters that had a much larger surface area per unit mass, which might cause staining when their interface was not perfectly silanized and integrated into the resin (23). Ertaş et al. (24) found that FU nanofill composite demonstrated more color changes than composites of the same manufacturer with nearly the same composition and practically the same filler loading by volume. They stated that this might be due to the relatively high water absorption character of the agglomerated particles and nanoclusters present in Filtek Ultimate.

Water storage alone does not cause more than one point of color change (25). However, chemical changes in the material may lead to a decrease in the resistance to staining (26). Excessive water absorption causes the deformation of the resin structure and the formation of microcracks by hydrolysis of silane. Subsequently, the dyeing agents can seep into the microcracks between the filler-resin matrix and the interfacial spaces and cause discoloration (27). Changes in the formulation of composite resins, such as organic matrix components, amounts and sizes of inorganic filler particles, affect water absorption and therefore color stability.

The changes in formulations of resin-based composites, including organic matrix components, amounts and sizes of inorganic filler particles, affect their water absorption and hence color stability.

On the other hand the most important factor causing extrinsic discoloration of composite resins is surface roughness, which causes biofilm accumulation. Good finishing and polishing operations reduce surface roughness. There are important studies in the literature suggesting that aluminum oxide discs can be used to obtain smoother surfaces because they abrade filler particles and resin matrices at the same rate (28,29). Barbosa et al. (30) stated that they might be acceptable as a clinical standard for polishing composites. In this study, OneGloss (Shofu) polishing rubbers containing aluminum oxide particles were used but the surface roughness of the samples was not measured.

Coffee has been shown to cause significant color change in composite resins in some previous studies (3,12). As coffee is a dark solution, it has a large amount of pigment that can accumulate in the structure of the restorative, absorbing more light and causing more opacity by increasing light diffusion (31). Similarly, in the present study, coffee caused statistically significantly more coloration for all resin-based composites compared to samples stored in water. GC Enamel stained more than all resins. Therefore, the first hypothesis of our study was rejected. In other words, a difference was found between the color stability of the composite resins subjected to the staining process. The difference between the ΔE values of other composite resins except GC Enamel was not statistically significant.

The samples in some studies were not kept in continuing contact with the staining solution, to reflect the clinical situation more closely (32,33). Similarly, in this study, samples were kept in coffee solution for forty five minutes a day, and in distilled water for the rest of the day. Then, the samples subjected to coffee staining for 14 days were brushed for 45 seconds with an electrical toothbrush and whitening toothpaste. Whitening toothpastes remove extrinsic stains on the tooth surface by means of some abrasive and whitening substances. Generally, commercial whitening toothpastes use pyrophosphate as the whitening agent, but Colgate Optic White toothpaste also contains hydrogen peroxide. It also contains silica as an abrasive (34).

In this study, the translucency of the resins was not measured, but generally the resins ranged from less translucent to more translucent in the order of opaque, dentin, body, enamel (12). In the present study, GC Enamel was statistically significantly more stained with coffee than GC Dentine. Thus, the second hypothesis of our study was also rejected. In other words, translucency affected the color stability of resin based composites.

The third hypothesis of our study was also rejected. Because, after brushing, ΔE values of GC Enamel and IED Enamel were statistically significantly higher than other resins.

When composite resins of the same brand were compared within themselves, the color change values of the enamel shades were the highest after both staining and brushing, for all commercial brands, except CX enamel after staining. These results are consistent with the results of the study of Salgado et al. (3) in which they found that high translucent materials had the lowest color stability for all commercial composite brands they used in their study.

These results may be related to the protocol of the study. In the present study, all surfaces of the samples were exposed to coffee solution and color measurements were made on a white background. Since the enamel shades were more translucent, it might cause the stains on the back of the samples to be determined more than opaque resins. This speculation may be more likely for the period after brushing in which the stains on the upper surface of the specimens have been removed. In this study, also the ΔE values of IED Enamel were not statistically different from other resins after staining, but were higher after brushing. In compatible with this explanation, in a study evaluating the translucency of resins, lower lightness, lower croma, higher hue presented by more translucent shades were associated with the increased black background effect as a result of the increased translucency (3).

Additionally, another study showed that less chromatic composite resin shades tended to have less color stability than shades that were more chromatic (35). It was stated that pigments and unreacted and subsequently oxidized contents might compromise optical stability due to the possibility that they became more pronounced in resins with high translucency (12).

On the other hand, the translucency of composites is determined by macroscopic phenomena such as monomer properties, content and composition of filler particles, as well as relatively small pigment additions and potentially all other chemical components (10). These chemical differences that affect the translucency can also affect the color stability of the resins.

The amount of color change of dentin and body shades differed according to the brands. When composite resins of the same brand were compared within themselves, although the difference between them was not statistically significant, the order of ΔE values in both staining and brushing groups was body > dentin for ESQ and CX and it is dentin > body for FU.

Except CX Dentin, the ΔE values after brushing for all composite resins were lower than the ΔE values after staining, but higher than the ΔE values of water storage group. In other words, brushing with whitening toothpaste removed some of the coffee discoloration, but failed to achieve the color change values in samples not subjected to coffee solutions. Although this result was also valid for opaque resins such as dentin, which might prevent the discoloration of the back surface of the sample from being seen, the reason for these results might be that the lower surfaces of the samples were not brushed. Another reason for these results may be that as Jonier states, although it is possible to remove the external stain by brushing, internal stains may remain (36).

Surface roughness of a sample affects instrumental color coordinates. Under diffuse reflection conditions measured by spectrophotometer, resin composites with a rough surface appear lighter and less chromatic than those with a smooth surface (37). In our study, even 14 days of brushing simulation may have increased the surface roughness and had an effect on color change. Studies in the literature have generally examined the effect of long-term tooth brushing simulations on the surface roughness of composite resins (38-40). In a study, different color and surface roughness values were observed in composite resins that were subjected to tooth brushing in situ with a whitening toothpaste for a relatively short time (90 days) as in our study (41). In the same study, it was reported that whitening toothpastes were not associated with color change on the composite. However, the abrasiveness of whitening toothpastes affects the surface roughness of different restorative materials.

It is also important to state that in vitro studies have limitations. In this in vitro study, different translucent/opaque shades were evaluated separately, but it should be aware that the use of different pastes by layering will change the current outcomes. In addition, there are many variables that can affect the overall appearance and color stability of the restorations, such as the operator's knowledge and skills regarding the restorative procedure, and the patient himself/herself eating and staining beverages' consumption habits and oral hygiene habits.

### Study Limitations

The limitation of this study was that color measurements made on a white background were more likely to cause stains on the back of the samples to be detected more than opaque resins, due to the more transparent enamel tones.

## Conclusion

Storage in water had minor effects on color stability, while subjected to coffee had a more important effect. There was no significant difference in color stability between resin-based composite brands. The translucent shades of the same brand, enamel shades, showed the greatest color changes, but the amount of color change of dentin and body shades differed according to the brands. The color change values of the samples subjected to the coffee solution decreased significantly after brushing with the whitening toothpaste, but these values were still greater than the color change values of the samples not subjected to the coffee solution.

### Ethics

**Ethics Committee Approval:** *In vitro* study.

**Informed Consent:** *In vitro* study.

**Peer-review:** Externally peer reviewed.

**Authorship Contributions**

Concept: N.Ç., F.S.G., O.F.A., M.S.V., E.C.Ş.B., Design: N.Ç., F.S.G., O.F.A., M.S.V., E.C.Ş.B., Data Collection or Processing: N.Ç., F.S.G., O.F.A., M.S.V., E.C.Ş.B., Analysis or Interpretation: N.Ç., F.S.G., O.F.A., M.S.V., E.C.Ş.B., Literature Search: N.Ç., F.S.G., O.F.A., M.S.V., E.C.Ş.B., Writing: N.Ç., F.S.G., O.F.A., M.S.V., E.C.Ş.B.

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Original Article

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# Short-term Effect of Elastic Taping on Balance and Postural Control in Patients with Early-stage Parkinson's Disease -a Non-controlled, Quasi-experimental Study

## Erken-evre Parkinson Hastalarında Elastik Bantlamanın Denge ve Postüral Kontrol Üzerine Kısa Süreli Etkisi-kontrolsüz, Yarı Deneysel Bir Çalışma

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## ABSTRACT

**Objective:** Normal postural control and balance is achieved by the integration of visual, proprioceptive and vestibular sensory information. The patients with Parkinson's disease (PD), on the other hand, experience postural control disorders due to the lack of integration of these senses. Elastic taping is effective in improving expected postural adjustments by increasing proprioception and trunk muscle activation. The aim of this study was to investigate the short term effect of single session elastic taping on balance and postural control in patients with early-stage PD.

**Methods:** Elastic tape was applied with posture correction techniques on the upper back of 23 patients with early-stage PD (18 men, 5 women) during "on" phase. The postural control and balance ability of patients was assessed with the limits of stability (LOS), Sit-to Stand, Walk Across and Tandem Walking Tests of NeuroCom Balance Master test device. The tests were repeated after elastic taping in all patients.

**Results:** The maximum excursions and endpoint scores of LOS test, the speed of tandem walking test significantly increased after taping (Wilcoxon test, respectively; p=0.04, p=0.02, p<0.001). There was no significant difference between Walk Across and Sit to Stand results before and after elastic taping (Wilcoxon test, p>0.05).

## ÖZ

**Amaç:** Görsel, proprioseptif ve vestibüler duyusal bilgilerin integrasyonu ile normal postüral kontrol ve denge sağlanır. Parkinson hastaları (PH) ise bu duyuların integrasyonu yetersizliği nedeniyle postüral kontrol bozuklukları yaşarlar. Elastik bantlama, propriosepsiyonu ve gövde kaslarının aktivasyonunu artırarak beklenen postüral ayarlamaları iyileştirmede etkilidir. Bu çalışmanın amacı, erken evre PH'lerinde tek seans elastik bantlamanın denge ve postüral kontrol üzerindeki kısa süreli etkisini araştırmaktı.

**Yöntemler:** Erken evre 23 PH'nin (18 erkek, 5 kadın) "On" döneminde, üst sırt bölgesine postür düzeltme teknikleri ile elastik bant uygulandı. NeuroCom Balance Master test cihazının kararlılık sınırları (LOS), Otur Kalk, Normal Yürüme ve Topuk Parmak Ucu yürüme testleri ile hastaların postüral kontrol ve denge yetenekleri değerlendirildi. Tüm PH'de elastik bantlama sonrası testler tekrarlandı.

**Bulgular:** Bantlamadan sonra LOS testinin ulaşılan maksimum uzaklık ve ulaşılan son nokta puanları ve Topuk Parmak Ucu Yürüme testinin hızı anlamlı olarak arttı (Wilcoxon testi, sırasıyla; p=0,04, p=0,02, p<0,001). Elastik bantlama öncesi ve sonrası Normal Yürüme ve Otur Kalk testi sonuçları arasında anlamlı bir fark yoktu (Wilcoxon testi, p>0,05).

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**ABSTRACT**

**Conclusion:** Our study is the first to investigate the short-term effects of elastic taping on balance and postural control in PD. It was concluded that the application of elastic tape in patients with PD could enhance dynamic balance and postural control parameters for a short time under challenging and complex conditions.

**Keywords:** Parkinson's disease, tape, balance, postural control, short-term

**ÖZ**

**Sonuç:** Çalışmamız, PH'de elastik bantlamanın denge ve postüral kontrol üzerindeki kısa süreli etkilerini araştıran ilk çalışmadır. PH'de elastik bant uygulamasının zorlu karmaşık koşullar altında dinamik denge ve postüral kontrol parametrelerini kısa bir süre için iyileştirebileceği sonucuna varılmıştır.

**Anahtar Sözcükler:** Parkinson hastalığı, bant, denge, postüral kontrol, kısa süreli

## Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized with motor, cognitive, emotional, autonomic and sensory impairments (1). Postural instability and balance impairment, which become evident as the disease progresses, could also be seen in the early-stage (2). Song et al. (3) reported that balance and postural control deficiencies could be detected in patients with early-stage PD by the use of evaluations involving complex tasks that challenged the neuromuscular system.

It is thought that in patients with PD, changes in the perception of verticalization due to impaired proprioception and somatosensory integration disorders, which lead to static and dynamic postural instability (4,5). Therefore, therapeutic approaches including active posture correction and proprioceptive stimulation are thought to be effective on axial symptoms (6).

In patients with PD, the reduced spinal movements cause an effort to maintain the body gravity line within the limits of stability and are usually compensated by increased trunk flexion which results in imbalance (4,5). Increased trunk flexion and the change in scapular position cause prolonged stress on muscle and joint structures, resulting in proprioceptive loss (7). It is known that even if there are no clinical findings of postural instability, postural synergies and hence postural control decrease in patients with early-stage PD especially under active challenging conditions (2,3).

Elastic taping aims to activate the proprioceptive system by increasing sensory stimuli with cutaneous mechanoreceptors, to improve anticipatory postural adjustments and activate trunk muscles and joints without restricting body movements. In the literature, it was showed that application of elastic taping on low back in non-specific chronic low back pain patients improved postural control in a short time period and elastic taping for postural correction in osteoporosis-associated thoracic kyphosis patients immediately improved the balance parameters (8,9). Studies have shown that elastic taping improves postural control and balance not only by increasing proprioceptive sensation, but also by determining the correct joint position for a comfortable and non-burdening posture (7,10). In recent years, it has been utilized in musculoskeletal and neurological diseases with the aim of increasing or inhibiting muscle activity, providing joint repositioning, preventing injuries and improving proprioception (11,12).

In the literature, within our knowledge, there are no studies examining the short-term effects of elastic taping on balance and postural control in patients with PD. Therefore, in this study, we aimed to investigate the short-term effects of single session elastic taping on balance and postural control in patients with early-stage PD. The hypothesis of the present study was that the application of single session elastic taping in patients with early-stage PD would improve balance and postural control in a short-term period.

## Methods

### Study Design

### Participants

This study was carried out between February 2017 and June 2018 in Dokuz Eylül University, Faculty of Physiotherapy and Rehabilitation in cooperation with the Faculty of Medicine, Department of Neurology at Dokuz Eylül University. Patients who were diagnosed as having PD according to criteria of United Kingdom PD Society Brain Bank, had a Mini-Mental test score of ≥24, a modified Hoehn&Yahr scale score of ≤2, were aged ≥18 years and who were able to stand independently for minimum 1 minute and walk for at least 10 meters without any support and had stable clinical status were included the study. The exclusion criteria were neurological, orthopedic or visual dysfunctions irrelevant of PD, affecting walking and balance ability.

### Ethics Approval

This study was approved by the Ethics Committee of Dokuz Eylül University with the protocol number 3013-GOA and decision number 2016/29-19. The objectives and methods were read to the patients who met the inclusion criteria and agreed to participate in the study, and an informed consent form was signed. This study was conducted in accordance with the Declaration of Helsinki.

### Sample Size

The sample size calculation was based on a similar study which examined the short term effects of elastic taping on balance in elderly with postural hyper kyphosis (for Limits of Stability outcomes) (13). The sample size was determined as 15 subjects using Epi Info TM 7 (7.1.1.14) program based on 95% confidence interval, 80% power rate and 0.05 Type 1 error.

**Intervention**

All patients were assessed before and after elastic taping application during the "on" phase. A physiotherapist who was trained and certified in taping, applied Kinesio Tex Gold FP elastic tape (5 cm) on the upper back of individuals with posture correction technique. The waterproof, porous, adhesive, 0.5 mm-thick tape was applied. This method was the application of a chemical-free elastic tape that mimiced the tissue and elasticity of human skin. Taping was applied starting from the acromioclavicular joint without stretching and went on with maximum stretching to the level of the thoracic 7$^{th}$ vertebra. Taping was terminated without stretching after 7 thoracic vertebrae levels. Two I-shaped elastic tapes were applied diagonally from the anterior of the right and left acromion towards the back (14). The subjects were re-assessed after a resting period for approximately 45 minutes. The application of elastic tape is shown in Figure 1.

**Measurement Methods**

The modified Hoehn & Yahr scale was used to evaluate the clinical characteristics of patients with PD. Stage 1 indicates the lowest level of disease severity, whereas stage 5 refers to the highest level (15,16). Participants with a Hoehn&Yahr score greater than 2 were excluded.

**Objective Balance Assessment**

The postural control and balance ability of patients were evaluated by using NeuroCom Balance Master device (NeuroCom System Version 8.1.0, B 100718, 1989-2004 NeuroCom® International Inc. USA) which measured the dynamic and static balance abilities (17). It has high test-retest reliability in assessing the postural stability and balance impairment of healthy individuals (18). It is a valid and reliable method to measure balance performance in patients with PD (19). The Balance Master consisted of 48.26x152.40 cm$^2$ force plate connected to a computer including a software program that calculated the center of pressure relative to the platform coordinates. Force data were sampled at a frequency of 100 Hz. The objective balance assessments took place in a room free from external distractions. Before the assessment, the patients were positioned at standardized foot position on the force plate (Medial malleolus in horizontal line, calcaneus in vertical line). Before the objective balance assessment, trial tests of all evaluation parameters were performed for each patient in order to help the patients get used to the Balance Master device and to reduce the learning effect.

**Postural Control**

**Limits of Stability (LOS)**

The patient was asked to move the center of gravity as quickly as possible to 8 different targets (anterior-posterior, right-left and other directions) displayed on the computer screen while standing stationary above the center point determined on the platform. The time spent by patients for body moves (reaction time, sec.), the movement velocity (%/sec.), the last point that the subject could reach the target point (endpoint excursions, %), the distance to the target point (maximum excursions, %), and the linearity of the movement while moving towards the target point (directional control, %) were measured (20).

**Balance**

**Tandem Walk Test**

The patient was instructed to walk with tandem steps and stand stable at the end of the platform. The step width (cm), walking speed (cm/sec), and postural sways at the end of the pathway (deg/sec) were measured. Each test was repeated 3 times 20.

**Walk Across Test**

Step width (cm), step length (cm), and walking speed (cm/sec) were measured while the patient was walking on the platform at the speed which they felt comfortable and safe. Each test was repeated 3 times (20).

**Sit-to-Stand Test**

The patient stood up quickly from the 40.64 cm high platform he/she was sitting on without using her/his arms or hands and waited for 5 seconds for the sway of the center of gravity to be measured. The time from sitting to standing stable (sec), the index of body weight rising (%), the speed of the sway of center of gravity while standing stable (°/sec), and the body weight's symmetry to right or left (%) were measured. Each test was repeated 3 times (20).

**Statistical Analysis**

The statistical analysis in this study was performed using "Statistical Package for Social Sciences" (SPSS) Version 22.0 (SPSS inc. Chicago, IL, ABD) program. The results were

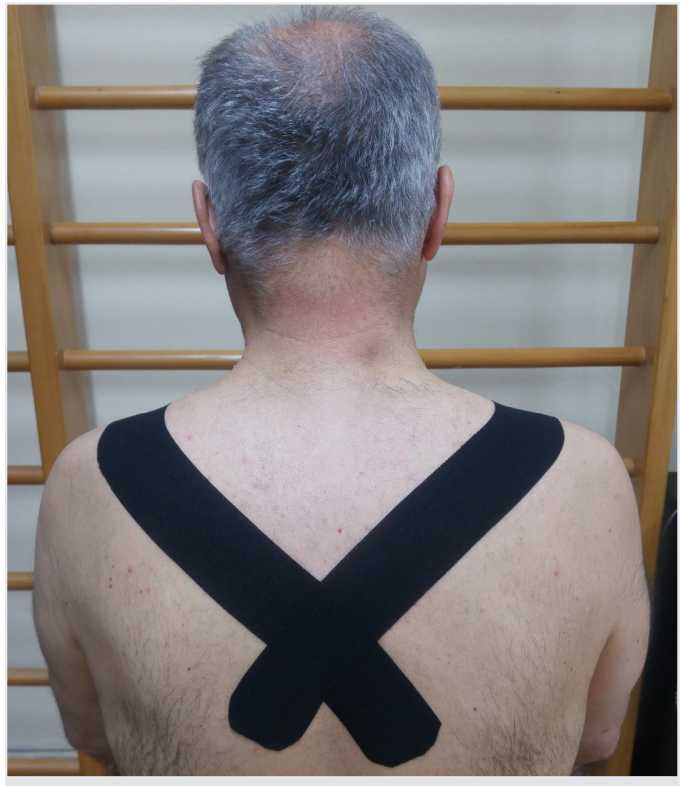

**Figure 1.** The application of elastic tape

presented as means and standard deviation. Wilcoxon test was performed to compare the difference between the results before and after the elastic taping application. P<0.05 was accepted to be statistically significant (21).

## Results

In total, 23 patients with PD (18 males and 5 females) participated in the study. There was no allergic reaction in the patients after the application of elastic taping. The mean age of the patients was 64.52±6.28 years. Table 1 illustrates the demographic characteristics of the patients.

There was no significant difference between before and after taping outcomes of reaction time, movement speed and movement control parameters in terms of LOS test (p>0.05). The maximum excursion and endpoint values increased significantly after taping in patients with PD (p<0.05, Table 2).

There was no significant difference between before and after taping values of Walk Across and Sit to Stand Tests. The walking speed of tandem walk test decreased significantly after taping (p<0.05, Table 3).

## Discussion

The aim of this study was to determine the effects of single session elastic taping on dynamic balance and postural control parameters in patients with early-stage PD. The main result of our study was that the short-term effect of elastic taping on postural control and balance occurred in active and challenging conditions such as tandem walking and stability limits. The walking speed in Tandem Walk test, maximum excursions and endpoint values in LOS test increased after elastic taping application.

Recognizing and evaluating impairment in balance and postural control are so important in the management of PD, as it directly affects walking, mobility, and falls (22). Since it is difficult to identify balance and postural control deficits in early-stage PD, it is thought that fall and balance disorders usually occur in the late stages of the disease (23-25). In the literature, it was reported that balance and postural control disorders occurred in early-stages of PD, but clinical tests were not sufficient to detect this, and advanced computerized static and dynamic postural stability assessments (like posturography or accelometer) provided more accurate parameters (24-26). Based on this information, we preferred to analyze the LOS test, Tandem Walk test, Walk Across test and Sit to Stand test data of the patients with the Balance Master System in our study. Based on this information, we preferred to analyze the LOS test, Tandem Walk test, Walk Across test and Sit to Stand test data of the patients with the Balance Master System in our study. Supportive approaches such as exercise and elastic taping to be applied after computerized balance and postural control evaluations in the early-stage of PD, may be effective in improving balance and postural control disorders and slowing the clinical course, by supporting the correct posture. It has been stated in recent studies that elastic taping can be used for postural correction and can be an effective form of cutaneous proprioceptive biofeedback (7). Therefore, in our study, we applied elastic tape with the postural correction technique

**Table 1.** Characteristics of patients

| | | n =23 |
|---|---|---|
| Gender<br>n (%) | Male<br>Female | 18 (78.3)<br>5 (21.7) |
| Age (year) | | 65.0 (61.0-67.0) |
| Height (cm) | | 1.72 (1.65-1.78) |
| Weight (kg) | | 80.0 (75.0-92.0) |
| Duration of illness (months) | | 36.0 (11.0-48.0) |
| Modified Hoehn and Yahr | | 2.0 (2.0-2.0) |
| All data were given as median (interquartile range) | | |

**Table 2.** A comparison of postural control measurements before and after elastic taping application

| | n=23<br>Median (interquartile range) | | |
|---|---|---|---|
| | Before elastic taping | After elastic taping | P |
| LOS reaction time (sec) | 0.37 (0.26-0.59) | 0.33 (0.17-0.47) | 0.19 |
| LOS movement velocity (deg/sec) | 2.7 (2.2-3.4) | 2.9 (2.5-3.6) | 0.19 |
| LOS endpoint (%) | 64 (59-75) | 71 (63-81) | 0.02* |
| LOS max excursions (ESM) (%) | 82 (74-88) | 85 (78-91) | 0.04* |
| LOS direction control (%) | 76 (66-79) | 73 (66-79) | 0.59 |
| *Wilcoxon test, p<0.05 | | | |

to the upper back of patients with early-stage PD in order to increase proprioceptive feedback and support correct posture.

Postural stabilization is provided by the passive support of the osteoligamentous system, active support of the musculotendinous system and neural control. In PD, it is assumed that postural disorders develop due to musculotendinous changes such as decreased muscle flexibility, muscle endurance and muscle weakness and deficiency in neural control, therefore applications on the upper back area for these changes are thought to help improve posture (27). It has been shown that the active musculotendinous system and the neural control components of spinal stabilization are improved with the application of elastic banding, which contributes to postural control and affects the proprioceptive system in neurological diseases, thus supporting the spine in a neutral position (28,29). Elastic taping stimulates proprioceptive receptors by increasing motor nerve excitability and regulating muscle activity, and provides feedback on posture, thus increasing postural awareness during daily activities. Elastic taping has been shown to improve postural control and balance not only by increasing the proprioceptive sensation but also by determining the correct joint position for a comfortable, no weight-bearing posture (7,10,11,28).

When studies evaluating the short-term effect of upper back elastic taping in different disease groups were examined, it was observed that the effect of taping on the angle of kyphosis was frequently examined (9,13,14). However, in our study, kyphosis assessment was not performed because balance and postural control were evaluated in patients with early-stage PD who did not develop postural deformities. Greig et al. (14) reported that the decrease in the kyphosis angle they detected after taping could be due to the passive support of the tape and the active support of muscle contraction. In another study, it was reported that elastic taping helped to correct posture and increased stability limits in kyphotic elderly individuals (13). On the contrary, Bulut et al. (9) reported that similar elastic taping application did not have a significant short-term effect on kyphosis angle and clinical balance values in women with postmenopausal osteoporosis-associated thoracic kyphosis. Since there are few studies and conflicting results in the literature regarding the short-term effect of upper back elastic taping applied for postural correction, we think that our study can summarize and clarify the findings in the literature on this subject. As stated in other studies, it was found in our study that the application of upper back elastic taping did not have an influence on simple balance and postural control tasks, but improved the performance of challenging balance and postural control in such conditions as stability limits and tandem walking.

Elastic taping can improve poor proprioception by increasing sensory input via cutaneous mechanoreceptors. Therefore, patients with poor proprioception, such as PD, may benefit more than healthy individuals with good proprioception (30). It has been reported in studies that short-term elastic tape application on the lower back improves the trunk position sense and trunk postural control in healthy women (31). There are few studies emphasizing that elastic taping applied to the upper back can change balance and postural stability parameters in a short time in stroke, another neurological disease in which proprioception is reduced, but there are no studies examining this in PD (29,32,33). Therefore, in our study, we investigated the short-term effects of elastic taping on balance and postural control. In our study, the short-term effect of elastic taping, which we applied for a single session, emerged in active and challenging conditions such as tandem walking and stability limits. After the application, walking speed in the Tandem Walk test, maximum excursions and endpoint values in the LOS test increased.

The improvement in the values of the LOS test, which evaluates postural control by measuring the active stability limits of the individual, indicates better balance and postural control (19,34). As the disease stage progresses in PD, LOS parameters worsen (movement speed decreases, endpoint and maximum excursion values decrease significantly) and the risk of falling increases with the increase in trunk rigidity and decrease in trunk coordination

**Table 3.** A comparison of balance measurements before and after elastic taping application

| | n=23<br>Median (interquartile range) | | |
|---|---|---|---|
| | Before elastic taping | After elastic taping | P |
| Walk across step width (cm) | 17 (14.4-19.2) | 15.6 (13.5-19.3) | 0.85 |
| Walk across step length (cm) | 49.9 (44.3-57.6) | 54.3 (43.4-61.7) | 1.00 |
| Walk across speed (cm/sec) | 64.3 (56.5-72.4) | 61.2 (52.8-73.1) | 0.74 |
| Walk across symmetry (%) | 13 (4-19) | 13 (8-22) | 0.35 |
| Sit to stand weight transfer (sec) | 0.41 (0.29-0.63) | 0.41 (0.29-0.55) | 0.50 |
| Sit to stand sway velocity (deg/sec) | 3.3 (2.5-4.2) | 3.4 (2.9-4.3) | 0.87 |
| Sit to stand rising index (%) | 22 (18-25) | 20 (18-26) | 0.77 |
| Sit to stand symmetry (%) | 10 (5-13) | 8 (4-17) | 0.85 |
| TANDEM step width (cm) | 8.9 (7.8-11.2) | 9 (8.3-12.0) | 0.63 |
| TANDEM speed (cm/sec) | 26.9 (22-30.6) | 33.1 (27.3-35.8) | <0.001* |
| TANDEM end sway (deg/sec) | 4.8 (3.5-5.9) | 4.0 (3.0-5.0) | 0.12 |

*Wilcoxon test, p<0.05

(19,34). The improvement in this test performance after some rehabilitation approaches used in PD reflects the improvement in postural strategy. All rehabilitation approaches that will improve the LOS parameters are important in order to increase the independence of the patients in daily life and to reduce the risk of falling. It is thought that elastic taping, which is one of these approaches, can improve the anticipatory postural adjustments and increase postural stability by increasing proprioceptive stimulation in neurological patients. When the studies investigating the short-term effect of elastic taping in neurological diseases were examined, it was stated that calf taping in patients with Multiple Sclerosis reduced postural instability by improving the standing balance. It has been reported that ankle taping increases stability limits in patients with stroke, and trunk taping improves dynamic balance and dynamic postural control (32,35,36). Unlike other studies, in our study, elastic taping was applied to the upper back and only the maximum excursions and the end point values were observed to significantly increase. Elastic taping may have provided a biomechanical advantage with increased proprioceptive input in challenging conditions such as reaching the end point of stability limits in patients. Poor performance of an individual with PD in the LOS test indicates that the individual's functionality decreases and the risk of falling increases. Since patients cannot move their trunks correctly within the limits of stability, they experience imbalance during activities of daily living in which body weight is displaced, such as walking and reaching for objects (19,37). We think that the elastic tape, which can stay on the skin up to 1 week after application, will provide proprioceptive support to the patients, especially in dynamic and challenging conditions such as reaching, walking, sitting and standing in daily life and will help them to perform these functions without experiencing imbalance.

In the only study in the literature in which elastic taping was applied in PD, it was stated that taping applied within the scope of postural rehabilitation program (stretching, postural training, proprioceptive discrimination exercises and elastic taping to the trunk) did not affect dynamic balance performances (measured with Timed Up and Go and Berg Balance scale) (38). In our study, in which we applied elastic taping to increase postural control and to give proprioceptive input to the trunk, taping had no effect on dynamic balance values such as STS and NWT, but a significant increase was observed in tandem gait speed. Elastic taping made a significant difference in dynamic balance values only in this test because the tasks in the TWT were more demanding than in other tests, and patients with early-stage PD showed imbalance, especially in active and challenging conditions (39). However, tandem walking is a determinant of general mobility and walking difficulties in PD. Difficulty in walking in tandem is more pronounced in advanced stages of PD, where overall mobility decreases and the risk of falling increases (40). For this reason, applications that can be made to improve this gait before the disease stage progresses are important. This increase in tandem walking speed in our study shows us that elastic taping may be beneficial on bradykinesia in PD.

**Study Limitations**

The lack of a control group is the most important limitation of this study. Follow-up studies involving a control group matched for age and disease stage are required to reduce placebo effects and bias. In these studies, it would be beneficial to make a sham application to blind the subjects to the treatment distribution and to reduce the risk of compliance.

**Conclusion**

Although there are many studies in the literature examining the short-term effect of elastic taping in different disease groups, our study is the first to investigate the short term effects of elastic taping on balance and postural control in PD. It is stated in the literature that the decrease in the LOS test endpoint and maximum excursion and TWT walking speed values typically indicate balance problems, poor postural control ability, and bradykinesia in patients with PD. In our study, we observed a short-term improvement in these parameters after taping. In the light of all this information, our study offers physiotherapists an alternative method, elastic taping, which can be effective in improving balance and postural control in the early-stage of PD. We think that our study will offer an insight into other studies that will investigate elastic taping in PD in the future.

**Ethics**

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Dokuz Eylül University with the protocol number 3013-GOA and decision number 2016/29-19.

**Informed Consent:** The objectives and methods were read to the patients who met the inclusion criteria and agreed to participate in the study, and an informed consent form was signed.

**Peer-review:** Externally peer reviewed.

**Authorship Contributions**

Surgical and Medical Practices: E.G., B.D.Ç., R.Ç., B.B., Concept: E.G., B.D.Ç., R.Ç., B.B., Design: E.G., B.D.Ç., R.Ç., B.B., Data Collection or Processing: E.G., B.D.Ç., R.Ç., Analysis or Interpretation: E.G., B.D.Ç., Literature Search: E.G., B.D.Ç., Writing: E.G., B.D.Ç., R.Ç., B.B.

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Review

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# Aromatherapy in Cancer Patients Receiving Palliative Care

## Palyatif Bakım Alan Kanser Hastalarında Aromaterapi

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**ABSTRACT**

Palliative care is a specialty that aims to prevent and reduce the distress of patients and their families who encounter life-threatening diseases. Especially, it aims to eliminate the problems caused by the cancer itself or the treatment methods. Patients diagnosed as having cancer experience many problems such as nausea, vomiting, anxiety, depression and sleep disturbance due to the disease and its treatment. Patients can search for complementary treatment methods such as aromatherapy in order to reduce or eliminate these symptoms and increase their well-being and quality of life. Aromatherapy is defined as the use of essential oils obtained from plants for therapeutic purposes. Essential oils used in aromatherapy are applied in the form of massage, bath or inhalation. In this review, the use of aromatherapy in the treatment of common symptoms in cancer patients receiving palliative care will be discussed.

**Keywords:** Palliative care, cancer, aromatherapy

**ÖZ**

Palyatif bakım, yaşamı tehdit eden hastalıklarla karşılaşan hasta ve ailesinin sıkıntılarını önlemeyi ve azaltmayı amaçlayan bir uzmanlık alanıdır. Özellikle kanserin kendisinden veya tedavi yöntemlerinden kaynaklanan problemleri ortadan kaldırmayı amaçlar. Kanser tanısı konmuş hastalar, hastalık ve tedavisine bağlı bulantı, kusma, anksiyete, depresyon ve uyku bozukluğu gibi pek çok sorun yaşamaktadır. Hastalar bu semptomları azaltmak ya da ortadan kaldırmak, iyilik halini ve yaşam kalitesini artırmak amacıyla aromaterapi gibi tamamlayıcı tedavi yöntemlerine başvurabilmektedir. Aromaterapi, bitkilerden elde edilen uçucu yağların, terapötik amaçlı kullanılması olarak tanımlanmaktadır. Aromaterapide kullanılan uçucu yağlar masaj, banyo veya inhalasyon şeklinde uygulanmaktadır. Bu derlemede palyatif bakım alan kanser hastalarında yaygın olarak görülen semptomların iyileştirilmesinde aromaterapi kullanımına değinilecektir.

**Anahtar Sözcükler:** Palyatif bakım, kanser, aromaterapi

## Introduction

Palliative care is a multidisciplinary specialty that has gained importance in recent years and focuses on preventing and reducing the distress of patients and their families who encounter life-threatening diseases. It aims to help patients who need support at all stages of the disease and at the end of life. Palliative care is an approach that aims to eliminate the problems caused by cancer itself or treatment methods, and to increase the quality of life of patients and their relatives. In recent years, many reasons such as the increase in the incidence of cancer and the life span of individuals diagnosed as having cancer, and aggressive treatments in the last stages of life have increased the need for palliative care (1). American Society of Clinical Oncology (ASCO) defined palliative care in cancer patients as "integrating improvements in cancer care for various conditions that affect the quality of life that are painful and distressing for patients and their families" (2).

Today, cancer is one of the most important health problems (3). Cancer patients experience various physical complications (hair loss, nausea, vomiting, pain, fatigue, anorexia, malnutrition and

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weakness) and psychological complications (depression, stress and anxiety) that reduce their quality of life (4,5). Despite recent advances in cancer treatment and the use of various treatments such as surgery, chemotherapy, hormone therapy, radiotherapy, and immunotherapy or biological therapy, patients still suffer from these complications due to the lack of definitive treatment (6). Today, the use of treatments such as complementary medicine is widely preferred to alleviate cancer symptoms, given their naturalness, low risks, less complications, and lower costs (7).

According to the World Health Organization, 80% of cancer patients use complementary medicine methods (8). One of the most widely used complementary therapies is aromatherapy, which refers to the use of aromatic oils to protect and improve physical and mental health, and this method is preferred in many countries such as Switzerland, Germany, the United Kingdom, Canada and the United States (9).

Aromatherapy is used as a popular complementary medicine method in the treatment of many complications in various patients (7). In aromatherapy, essential oils obtained from aromatic plants can be applied in the form of inhalation, massage, diffusion, compresses or baths. After essential oils and their components enter the body through the nose, skin or mucous membranes, they reach the bloodstream and eventually the brain, causing various effects. The molecules in inhaled essential oils reach the olfactory receptors in the nose and bind to different parts of the receptors. Receptors convert odors into electrical impulses and these electrochemical messages, formed by the binding of molecules to the receptors, are transmitted to the limbic system via the olfactory bulb and olfactory pathway. These messages activate the memory and emotional responses through the hypothalamus, allowing the response to be sent to other parts of the brain and to the body, thus causing various physiological effects in the body. For example, it is known that some components in essential oils affect the release of substances such as dopamine, serotonin, noradrenaline and endorphins in the brain stem and thus exert an analgesic effect (10). Essential oil molecules, in topical applications, are absorbed through the pores of the skin and mix with the blood circulation and thus show their physiological and physical effects (11). Different studies have shown that aromatherapy is used to improve the complications of fatigue, depression, stress, anxiety, pain, sleep disorders, nausea and vomiting and increase the quality of life in cancer patients (7).

In this review, aromatherapy methods used to alleviate common symptoms such as nausea, vomiting, anxiety, depression, sleep disturbance and pain in cancer patients receiving palliative care will be examined.

**Nausea and Vomiting**

Nausea and vomiting are two of the most important gastrointestinal problems that seriously threaten the quality of life of palliative care patients. These symptoms appear due to the disease, due to the presence of cancer in the gastrointestinal tract, or as side effects of the treatments applied (12). Studies report that nausea and vomiting seen in cancer patients cause fluid-electrolyte imbalance, dehydration, weight loss, physiological effects caused by poor drug absorption, and decreased excretion from the kidneys. However, it has negative effects on the social life, work life, daily activities and psychological well-being of the patients. In addition, nausea and vomiting cause some patients to refuse or discontinue chemotherapy (13).

Despite the development of more effective antiemetic agents, nausea and vomiting continue to be among the most disturbing side effects of chemotherapy (14). Studies have documented that the incidence of acute and delayed nausea and vomiting after chemotherapy is higher than 50%, even after antiemetic prophylaxis (15,16). For this reason, it is recommended to use complementary therapies together with pharmacological treatments to reduce chemotherapy-induced nausea and vomiting (CINV) (17). Aromatherapy is one of the complementary therapies commonly used for this purpose. When studies are examined, the use of peppermint and ginger essential oils comes to the fore, especially in coping with CINV (13,18-22).

Aromatherapy with medicinal peppermint (*Mentha piperita* L.) essential oil is recommended as an effective complementary therapy for the treatment of postoperative nausea due to its antiemetic and antispasmodic effects. Studies have shown the effectiveness of *Mentha piperita* in reducing postoperative nausea and vomiting (23), chemotherapy-induced nausea (24), and colon spasms during colonoscopy (25,26) and after colostomy surgery (27). The potential benefits of medicinal peppermint essential oil and aromatherapy include rapid onset of action, no side effects, affordable cost, and easy use, so it is used as a traditional anti-nausea and vomiting medicine (28).

Eghbali et al. (22) conducted a randomized controlled clinical study to determine the effect of aromatherapy containing medicinal peppermint essential oil on nausea and vomiting in the acute phase (first 24 hours) of chemotherapy in 100 cancer patients. Patients with a definite diagnosis of breast cancer and receiving chemotherapy with drugs (cyclophosphamide and adriamycin) that caused moderate to severe nausea were included in the study and the patients were randomly divided into intervention (n=50) and control (n=50) groups. In addition to the standard drugs given by the doctor, the patients in the intervention group were asked to pour two drops of 100% medical peppermint essential oil on a tissue paper 3 times a day (morning, noon and night), put it on the collar of their clothing and breathe normally for 20 minutes. The patients in the control group, on the other hand, used saline in the same way instead of breathing peppermint oil for the specified time. As a result of the study, it was reported that the frequency of nausea and vomiting decreased in 76% of the patients in the aromatherapy group, and there was a significant difference between the intervention and control groups. According to this study, it was stated that the use of aromatherapy with the recommended dose of medicinal peppermint essential oil did not cause any side effects and could be used as a therapeutic method together with medical treatments to improve CINV (22).

The effects of peppermint oil on frequency of nausea, vomiting and retching, and severity of nausea were evaluated in another quasi-randomized controlled study involving 80 cancer patients who underwent different chemotherapy protocols and experienced nausea and vomiting after chemotherapy treatment. The patients were divided into 2 groups as intervention and control groups. In patients in the intervention group (n=36), in addition to routine antiemetic therapy, 3% peppermint oil (18 drops of peppermint oil in 30 mL of sweet almond oil) was administered three times a day (morning, afternoon and evening) for five days following chemotherapy administration to the point between the upper lip and the nose (filtrum), and the patients were asked to take a deep breath after applying the aromatic mixture. Only routine antiemetic treatment was applied to the patients in the control group (n=44). As a result of the study, it was reported that peppermint oil significantly reduced the frequency of nausea, vomiting, retching and the severity of nausea in cancer patients undergoing chemotherapy. For this reason, the authors recommended the use of peppermint oil with antiemetics after chemotherapy, which had a medium and low emetic risk, to cope with CINV (13).

Mapp et al. (18) conducted a study with the participation of 79 patients and evaluated the effectiveness of peppermint essential oil against the intensity of nausea in cancer patients. The results of this study showed that the use of peppermint oil was effective in reducing the intensity of nausea experienced by patients compared to the control group (18). Although the sample size was low, in another study using peppermint oil to combat nausea in palliative care and hospice care, it was reported that the use of peppermint oil together with medical treatment reduced the frequency of nausea (19).

Ginger (*Zingiber officinale*), another herb of choice for dealing with CINV, has a long history in many cultures as a folk remedy for nausea and gastrointestinal ailments. Experimental research has shown that ginger can be effective as an anti-nausea agent; therefore, it has been suggested as a possible candidate for anti-CINV therapy (29). Although the exact mechanism of action is unknown, multiple active ingredients in ginger (gingerols, shogaol, zingiberen, zingerone, and paradol) have been found to exert potentially beneficial effects on many mechanisms involved in the pathophysiology of CINV. Cell culture and animal studies show that these components stimulate oral and gastric secretions (30,31), regulate gastrointestinal motility, and interact with 5-HT3 receptors involved in the CINV reflex (32).

In a study evaluating the effectiveness of ginger aromatherapy on nausea and vomiting in 60 patients with cervical cancer who received chemotherapy, the patients were divided into two groups as intervention (n=30) and control (n=30). The study groups were kept similar in terms of chemotherapy treatment protocol and antiemetic drug use. Patients in the intervention group were asked to add 5 drops of ginger oil to a mask and inhale this oil for 10 minutes, do this 30 minutes before starting the meal and repeat it when they felt nauseated. It was determined that the patients in the intervention group after the application were significantly less likely to experience nausea and vomiting than the control group. Therefore, the authors reported that ginger aromatherapy could be used as an alternative medicine to reduce nausea and vomiting after chemotherapy (20).

Lua and Zakaria (21) conducted a single-blind randomized controlled crossover study to evaluate the efficacy of inhaled ginger aromatherapy on nausea, vomiting, and health-related quality of life in 75 patients with breast cancer receiving chemotherapy. Patients received a 5-day aromatherapy treatment (at least 3 times a day, 2 drops) using ginger essential oil or ginger placebo (reduced therapeutic value, ginger fragrance oil). The patients were divided into 2 groups and the patients in Group 1 (n1=37) were given placebo (ginger essential oil) at the time of the first chemotherapy followed by ginger essential oil at the next chemotherapy. Patients randomized to group 2 (n2:38) were first given ginger essential oil at the time of the first chemotherapy and placebo (ginger fragrance oil) for the next treatment. As a result of the study, it was shown that aromatherapy applied as inhaled ginger essential oil for five days had limited effects in reducing CINV, other than alleviating acute nausea. The authors stated that the evidence from this study should be confirmed by further studies (17).

Zorba and Ozdemir (33) conducted a quasi-randomized controlled study with 75 patients with breast cancer to evaluate the effects of massage and inhalation aromatherapies on CINV. The patients were randomly divided into 3 groups as inhalation, massage and control. Patients in the massage group (n=25) received 20 minutes of aromatherapy foot massage before chemotherapy, while patients in the inhalation group (n=25) received 3 minutes of inhalation aromatherapy before chemotherapy. The control group (n=25) did not receive any treatment other than routine treatment and maintenance procedures. A mixture of English peppermint (*Mentha piperita*; 2%), bergamot (*Citrus bergamia*; 1%) and cardamom (*Elettaria cardamomum*; 1%) was used in 100 mL of sweet almond carrier oil for both inhalation and massage aromatherapy. The researchers followed the effects of aromatic mixture and massage applied before the 2$^{nd}$, 3$^{rd}$ and 4$^{th}$ chemotherapy courses on the severity of acute nausea after chemotherapy treatment. The severity of nausea was statistically significantly lower among the patients in the massage and inhalation groups than in the control group in all 3 cycles. In conclusion, the authors reported that massage and inhalation aromatherapy are promising for the treatment of CINV (33).

Another study involving 66 cancer patients suffering from CINV compared the effects of cardamom oil (*Elettaria cardamomum*) and inhalation aromatherapy on CINV versus placebo. Patients in the intervention group were asked to take deep 3 breaths twice a day, using pads impregnated with cardamom oil at 5-minute intervals. Distilled water was applied to the placebo group in the same way. In the follow-ups after the application, it was determined that the severity of nausea was significantly less in the intervention group than in the placebo group. As a result of the study, it was reported that inhalation aromatherapy with cardamom oil can be used to reduce the severity of chemotherapy-induced nausea in cancer patients (34).

In a study conducted with 60 cancer patients receiving chemotherapy with highly emetogenic agents, the effect of aromatherapy on CINV was examined. The patients were massaged with 6 drops of medicinal lavender oil (*Lavandula angustifolia*) for 10 minutes, starting from one hour before chemotherapy and every hour until the completion of chemotherapy, and inhalation of medicinal lavender oil was applied to the patients in addition to the massage. A significant decrease in nausea and vomiting was observed in each patient who received aromatherapy, and it was determined that the patients' nausea and vomiting levels decreased statistically significantly one day after chemotherapy administration compared to the control group ($p<0.01$). As a result of the study, it was stated that aromatherapy might be an effective option in the prevention and reduction of side effects such as nausea and vomiting experienced by cancer patients receiving chemotherapy with highly emetogenic agents (35).

**Anxiety and Depression**

Psychiatric symptoms such as hopelessness, anxiety and depression are common in palliative care patients. Studies show that 25-35% of cancer patients have significant anxiety or depression (36). Depression is a psychiatric disorder that is most common in hospices and palliative care units, especially in cancer patients, and its prevalence is at least 4 times higher than in the general population. It is an important health problem that should be handled carefully in palliative care units in terms of both its prevalence and its consequences (37). However, fear of death, worsening of quality of life and deterioration of social relations cause cancer patients to experience negative conditions such as anxiety and sleep disorders (38). Many pharmacological treatments are used to manage anxiety and depression, but these treatments can sometimes cause negative effects and economic loss. For this reason, complementary therapies such as participating in relaxation exercises, listening to music and aromatherapy can be used in the treatment of anxiety and depression in cancer patients (38).

Wilkinson et al. (39) investigated the effects of massage alone or aromatherapy massage on anxiety in 103 advanced cancer patients in a palliative care setting. The patients were randomly divided into two groups; one group (n=46) was given aromatherapy massage [with Roman chamomile oil (*Anthemis nobilis L.*)] for 3 weeks, while the other group (n=57) was only massaged for 3 weeks. The results showed a significant reduction in anxiety after each massage. Roman chamomile essential oil was shown to have beneficial effects on physical and psychological symptoms in advanced cancer patients. Researchers stated that massage with or without essential oils reduced anxiety levels, however, they concluded that the addition of an essential oil increased the effect of massage and improved physical and psychological symptoms and overall quality of life (39).

A randomized controlled trial was designed to compare the effects of four weeks of aromatherapy massage and massage alone on physical and psychological symptoms in 42 advanced cancer patients receiving palliative care in the UK. Fourty two patients were randomly divided into three groups. Aromatherapy massage group (n=16) was massaged with an inert carrier oil mixed with 1% medical lavender essential oil. The other group (n=13) was only massaged with an inert carrier oil, while the control group (n=13) did not receive any aromatherapy massage. The patients were given either only massage or aromatherapy massage for 30 minutes once a week for 4 weeks. In this study conducted with advanced cancer patients, it was stated that the difference between anxiety levels in aromatherapy massage group and massage only group was not statistically significant. While the level of depression did not change in the aromatherapy massage group, the depression levels decreased in the massage group only. The authors stated in this study that the addition of lavender essential oil did not increase the beneficial effects of massage, but patients with psychological disorders responded better to these treatments (40).

Santosh et al. (35) compared the anxiety levels of the control group with medical lavender oil massage applied together with medical lavender oil inhalation in patients receiving chemotherapy. In the study, it was found that anxiety levels decreased in both groups, and this decrease was statistically significantly higher in the group that received lavender aromatherapy ($p<0.001$) (35).

A clinical study was conducted to evaluate the effect of sweet orange essential oil (*Citrus aurantium L.*) on anxiety and included 42 patients with chronic myeloid leukemia (CML). Among the patients who were randomly divided into 3 groups, 10 mg of diazepam used as a standard anxiolytic drug was administered to the 1st group (n=14), 10 mL of sweet orange essential oil was administered to the 2nd group by inhalation for 30 minutes, and saline solution inhalation was applied for 30 minutes to the 3rd group (n=14), which was the placebo group. Evaluation was made with psychometric scales (STAI-S: State-Trait Anxiety Inventory), and a decrease in STAI-S scores was observed in the Sweet orange oil group, which was associated with anxiolytic effect. As a result of the study, it was observed that sweet orange oil showed anxiolytic effect and reduced anxiety-related signs and symptoms in CML patients (41).

Imanishi et al. (42) conducted a open semi-comparative trial to investigate the effect of aromatherapy massage with an essential oil mixture on psychological and immunological parameters in 12 patients with breast cancer. Aromatherapy massage (eight times in total) was applied to the patients twice a week for 4 weeks, using 30 minutes of Sweet orange oil (*Citrus aurantium*), lavender oil (*Lavandula angustifolia*) and Sandalwood oil (*Santalum album*). In the evaluations, it was shown that after the 5th and 8th sessions, the anxiety level of the patients decreased, the level of depression did not change, however, aromatherapy massage improved the immunological status. Researchers reported that aromatherapy massage was a complementary therapy that significantly reduced anxiety in patients with breast cancer (42).

A clinical study was conducted in 58 hospice patients to examine the effect of aromatherapy hand massage on pain, anxiety and depression in terminal cancer patients. The patients were randomly divided into two, and aromatherapy group (n=28)

was given 5 minutes of hand massage for 7 days with a mixture of Bergamot, Lavender and Frankincense diluted at the rate of 1.5% with sweet almond carrier oil (1:1:1 ratio). In the same way, hand massage was applied to the group (n=30) with only sweet almond carrier oil. The aromatherapy group showed significant differences in pain score (p=0.001) and changes in depression score (p=0.000) compared to the control group. According to the data obtained from the study, it was reported that aromatherapy hand massage had a positive effect on pain and depression in terminal cancer patients (43).

Anxiety is a common problem in patients in the preoperative period. In this context, in a randomized controlled study including 80 patients with breast cancer in whom breast surgery was planned, the effect of lavender oil inhalation on anxiety levels was investigated. The intervention group (n=40) was given gauze containing 3-4 drops of lavender oil (one drop of 0.1 mL at 100% concentration) for 20-minute inhalation on the day of surgery, while the control group (n=40) was given routine pre-surgical instructions. It was stated that both groups had similar levels of anxiety in the preoperative period, however, as a result of the study, the anxiety levels of the patients in the intervention group decreased significantly compared to the control group. According to the results of this study, it was reported that preoperative inhalation aromatherapy with medicinal lavender oil reduced anxiety levels (44).

In a randomized controlled study in which the effect of medicinal lavender oil aromatherapy on anxiety was evaluated in cancer patients receiving chemotherapy (such as breast cancer, lung cancer, ovarian cancer), patients were divided into 3 groups and lavender oil was administered to one group (n=30), tea tree oil aromatherapy was applied to another group (n=20), and no application was made to the control group (n=20). As a result of the study, it was shown that three drops of lavender oil inhaled every night before sleep decreased the anxiety levels of the patients and increased the quality of sleep. However, it was stated that tea tree oil had no effect on state and trait anxiety levels, but increased sleep quality. The authors compared the anxiety scores before and after chemotherapy and reported a statistically significant difference in the lavender group (45).

In a randomized controlled study, Khiewkhern et al. (46) examined the effects of aromatherapy massage (with coconut oil containing 0.05 mL ginger essential oil) for one week and three times a week, on anxiety and depression in patients with colorectal cancer. It was determined that the anxiety levels of the patients who received aromatherapy massage were statistically significantly reduced compared to the patients in the control group (p=0.001). However, there was no statistically significant difference between the groups in terms of depression level (46).

**Sleep Disorder**

Sleep disorders are one of the important health problems that negatively affect the quality of life in palliative care patients. The prevalence of insomnia, which is reported to be intense in 24-47% of patients in the literature, is reported to be 62% in palliative care patients (47,48). In this patient group, insomnia may increase the severity of other symptoms and negatively affect the quality of life of the individual (47). Many pharmacological and complementary therapies are used in the management of sleep disorders. Complementary treatments include music therapy, art therapy, progressive muscle relaxation exercises, yoga, massage, reflexology, food supplements, and aromatherapy (49).

It has been reported in various studies that medicinal lavender oil is used in the treatment of sleep problems due to their sleep-promoting effects and that it does not have any side effects (50-53). Studies have shown the sedative, anxiolytic, anticonvulsant, antiepileptic, spasmolytic and sleep-regulating effects of *Lavandula angustifolia* by suppressing the central nervous system (49). Because of all these properties, lavender is used for spiritual relaxation, therapeutic purposes (building physical and emotional well-being), and regulation of sleep disorders (45). In an experimental study with cancer patients, aromatherapy sticks containing different essential oils, including lavender, were placed around the patients, and as a result of the study, it was shown that the application of aromatherapy allowed the patients to relax, calm down and fall asleep (53).

Ozkaraman et al. (45) investigated the effect of lavender oil aromatherapy on sleep quality in cancer patients (such as breast cancer, lung cancer, ovarian cancer) undergoing chemotherapy in a randomized, controlled study. There was no significant change was observed in the Pittsburgh Sleep Quality Index (PSQI), which was used to measure sleep quality before and after chemotherapy in patients who were randomly assigned to the lavender oil group (n=30), tea tree oil group (n=20), and control group (n=20). As a result of the study, it was shown that three drops of lavender and tea tree oil inhaled every night before sleep increased the sleep quality of patients (45).

According to a recent study conducted to determine the effect of lavender oil on sleep quality and vital signs in 68 cancer patients receiving palliative care, while the medicinal lavender oil was applied to the patients (Before going to bed, they were asked to take 10 deep breaths of 3 mL of 100% pure lavender oil and the oil was left 1 m away from the patients overnight) in the experimental group (n=34) on the 2$^{nd}$ and 3$^{rd}$ days of the study, no application was made to the control group (n=34). It was observed that the application of lavender oil did not affect the vital signs of the patients, but provided deeper sleep on the 2$^{nd}$ day after the intervention, facilitated them to fall asleep and sleep again when they woke up, and increased their sleep quality. As a result of the study, it was stated that the use of lavender oil was an effective method to increase the overall sleep quality in palliative care patients and could be used safely in the management of sleep problems (49). In their randomized controlled study, Soden et al. (40) found that aromatherapy massage (with lavender essential oil) and classical massage applied to patients receiving palliative care statistically significantly reduced sleep problems.

*Rosa damascene* Mill (Isparta rose), which is used in the treatment of sleep disorders in cancer patients, is one of the most important species of the Rosaceae family (54). Clinical studies have shown

that *Rosa damascena* has a sedative effect without serious side effects (55,56). Heydarirad et al. (57) conducted a randomized, single-blind, controlled clinical trial to investigate the effect of aromatherapy containing two different concentrations of *Rosa damascena* essential oil on sleep quality in cancer patients. The patients were randomly divided into 3 groups, and each group was treated with rose essential oil at different doses (18 patients 5% rose essential oil in rapeseed oil, 18 patients 10% rose essential oil in rapeseed oil, and 18 patients control group) for 2 weeks at night. Aromatherapy treatment was given. Patients in the aromatherapy group were asked to apply the oil by inhalation for 20 minutes half an hour before going to bed for two weeks. The total PSQI scores used to evaluate sleep quality of both groups (5% and 10%) were found to be close and its effects were reported to be statistically significant compared to the control group. The authors stated that aromatherapy with *Rosa damascena* essential oil could be used as a suitable complementary therapy to improve sleep quality in cancer patients (57).

A double-blind, randomized, controlled clinical trial was conducted to investigate the effect of aromatherapy with diffusion of essential oils (lavender, peppermint, chamomile oil) on sleep and other common symptoms in hospitalized patients newly diagnosed as having acute leukemia. It was reported that aromatherapy application had a positive effect on sleep, and improvements in symptoms such as fatigue, lethargy, loss of appetite, depression and anxiety, which were common in patients, were noted. As a result of the study, it was reported that aromatherapy was a viable intervention to improve insomnia and other symptoms commonly experienced by patients with acute leukemia (58).

According to a randomized controlled study comparing the effect of inhalation aromatherapy with lavender and peppermint oil on the sleep quality of cancer patients, 120 patients included in the study were randomized to lavender (n=40), peppermint (n=40) and control (n=40) groups. Three drops of essential oil were dripped onto cotton for 7 days in the intervention groups, and they were adhered to the patient's collar for 20 minutes and the patients were allowed to breathe. Aromatic distilled water was applied to the control group in the same way. While the PSQI score averages used to determine the sleep quality of the patients did not show a significant difference between the three groups before the application, a statistically significant difference was found after the intervention. PSQI mean scores were lower in lavender and mint groups than in the control group. The results showed that inhalation aromatherapy with lavender and peppermint essential oils had the same effect on the sleep quality of cancer patients. Therefore, it has been reported that this simple and accessible method can be used to improve the sleep quality of cancer patients (59).

According to a randomized controlled clinical study involving 74 cancer patients treated in a palliative care setting, it was reported that a single session (30 minutes) of aromatherapy massage with essential oils (lavender oil, orange oil or a mixture of two oils) did not have a significant effect on improving sleep quality compared to the control group. This result was associated with a single session of massage and not evaluating the long-term effects in the study. Researchers noted that further clinical studies were needed to evaluate the long-term effects of aromatherapy massage (60).

**Pain**

Pain is a condition that is frequently seen in cancer patients, the most feared by patients and defined as "more terrible than death itself", and it significantly affects the quality of life and integrity of patients. Of cancer patients, 70% experience pain at any stage, and despite effective guidelines developed for the management of cancer pain, 80-90% are undertreated. It has been reported that 90% of patients receiving palliative care experience pain. Therefore, evaluation of pain at regular intervals and review of treatment are an important part of palliative care (61). It is known that due to the difficulties experienced in the evaluation and control of pain in cancer patients, patients frequently resort to complementary methods in addition to medical treatment (61). In the management of cancer pain; integrative methods such as reflexology, aromatherapy, massage, therapeutic touch, and reiki are frequently used to support medical treatment (62).

Pain and anxiety due to medical procedures performed in cancer patients can reduce the patient's compliance with the treatment and cause difficulties in the treatment procedure (63-65). In this context, a quasi-randomized controlled was conducted to examine the effects of inhalation aromatherapy on procedural pain and anxiety after needle insertion into an implantable central venous port catheter in cancer patients. In the study, which included 123 cancer patients who were planned to receive chemotherapy, the patients were randomly divided into the lavender group (n=41), the eucalyptus group (n=41) and the control group (n=41). Before inserting the needle into the implantable venous port catheter, the patients in the intervention group inhaled 3 drops of essential oil for 3 minutes, while the control group did not receive any application. At the end of the study, it was reported that the mean VAS scores of the lavender group were significantly lower than the control group ($p<0.05$), but there was no significant decrease in the VAS scores of the eucalyptus group compared to the control group ($p>0.05$). As a result, it has been stated that lavender essential oil is effective in reducing pain levels during the medical procedure due to its antinociceptive and analgesic properties, and inhalation aromatherapy with lavender can be used to reduce pain during the medical procedure (66).

İlter et al. (67) conducted a quasi-experimental study to evaluate the effect of inhalation aromatherapy on invasive pain, compliance with the procedure, vital signs, and saturation during port catheterization in 60 patients with cancer. For the patients in the intervention group (n=30), it was prepared by diluting orange, chamomile and lavender essential oils (1:1:1 ratio) in 70 mL distilled water, and this aromatic mixture was dripped onto the pillow and the patient inhaled for 15 minutes during the post-catheterization procedure. It was determined that inhalation aromatherapy applied to the patients in the intervention group reduced the pain experienced during the procedure and facilitated the compliance with the procedure; however, it was reported that it did not affect vital signs and saturation. As a result of the study, the

authors recommended the application of inhalation aromatherapy along with pharmacological treatments during the catheterization procedure, as it reduced invasive pain and facilitated compliance with the procedure (67).

In a quasi-experimental study conducted with chemotherapy-treated acute myeloid leukemia (AML) patients with a minimal pain score of 3, it was found that aromatherapy with 2% lavender oil reduced the pain intensity and there was a significant difference in pain intensity between the intervention and control groups (68).

In a randomized controlled study, Ovayolu et al. (69) included 280 patients with breast cancer receiving chemotherapy, and the effect of aromatherapy massage on patients' quality of life, physical and psychological symptoms, and cancer-related pain was investigated. In the aromatherapy massage group (n=70), aromatherapy massage was performed 3 times a week for 35 minutes for 1 month with a mixture of lavender, mint, chamomile, jasmine, violet, rosemary and eucalyptus essential oils (2:2:2:1:1:1:1 ratio) in 1.1% sweet almond oil. The classical massage group (n=70) was massaged by the same way with olive oil. The inhalation group (n=70) was given 5 minutes of inhalation of the aromatic mixture 3 times a week for 1 month, while no intervention was made in the control group (n=70). It was found that classical massage, aromatherapy massage and aromatherapy inhalation had positive effects on quality of life and physical and psychological symptoms, and especially aromatherapy massage was more effective. However, cancer-related pain levels were found to be significantly reduced in the aromatherapy group (69).

In their randomized controlled study, Khiewkhern et al. (46) found that there was a statistically significant decrease in pain levels in patients with colorectal cancer who received aromatherapy massage compared to the control group. In another study, it was reported that cancer patients who expressed pain before aromatherapy massage stated that they were relieved after the application (70). On the other hand, in a randomized controlled study conducted to investigate the effects of four-week aromatherapy massage and massage only on cancer-related pain in advanced cancer patients receiving palliative care, it was reported that there was no statistically significant difference between the pain levels of the group that received aromatherapy massage with lavender essential oil and the group that received only massage. In this study, it was reported that the addition of lavender essential oil did not increase the beneficial effects of massage, but patients with psychological disorders responded better to the treatment (40).

**Conclusion and Recommendations**

Patients in need of palliative care search for complementary methods such as aromatherapy in order to reduce their physical symptoms, control the side effects of treatment and improve their psychological health, in addition to their primary treatment. Aromatherapy is used to improve symptoms such as depression, anxiety, pain, sleep disorders, nausea and vomiting, which are commonly found in cancer patients receiving palliative care, and to increase their quality of life. The studies examining the effectiveness of aromatherapy in cancer patients receiving palliative care mentioned in our review and some of their findings are summarized in Table 1.

Chemotherapy-induced nausea and vomiting is among the most common and feared side effects of cancer treatments. Peppermint and ginger essential oils are the most researched aromatic oils for coping with CINV. In studies using different essential oils, aromatherapy has been shown to be effective in the treatment of CINV. In this context, it has been stated that aromatherapy can be used as a therapeutic method together with medical treatments to improve and prevent nausea and vomiting.

Anxiety and depression are among the most common complaints in cancer patients and palliative care patients. Lavender oil is the most studied essential oil in the treatment of anxiety and depression in cancer patients. Although the studies indicate that aromatherapy can be used to reduce anxiety and depression in cancer patients, on the other hand, the emergence of different results in studies examining the short and long-term effects of aromatherapy shows that there is a need for well-designed randomized controlled studies.

Another problem frequently encountered in palliative care patients is sleep disorders. One of the consequences of sleep disorders is its negative impact on quality of life and social functioning of the individual. Studies show that sleep disorders in cancer patients can lead to many problems such as fatigue, anxiety, depression and eventually cancer progression if not treated. The effectiveness of tea tree oil, rose oil, peppermint oil and chamomile oil, especially lavender oil, on sleep disorders in cancer patients has been demonstrated in clinical studies. For this reason, aromatherapy can make a positive contribution to the improvement of sleep disorders by adding it to the existing treatment in palliative care patients.

Pain is another common complaint in cancer patients that affects quality of life and integrity. Pain due to cancer or due to medical procedures can reduce the patient's compliance with the treatment and cause difficulties in the treatment procedure. The effectiveness of inhalation and massage aromatherapy applied with lavender, eucalyptus, chamomile and orange essential oils on pain in cancer patients has been supported by clinical studies.

As seen in the clinical studies mentioned in our review, aromatherapy can be used by cancer patients for short-term benefits to prevent nausea and vomiting, reduce pain, anxiety and depression, and improve sleep patterns and well-being. For this reason, it is recommended that aromatherapy be added to the existing treatment for prophylactic and therapeutic

**Table 1.** Studies examining the effectiveness of aromatherapy in palliative care and cancer patients and some of their findings

| Literature | Sample | Research design | Essential oil | Method of application | Symptom | Result |
|---|---|---|---|---|---|---|
| **Eghbali et al. (22)** | Group of patients with breast cancer receiving chemotherapy (n=100) | RCT | Peppermint oil | Dropping 2 drops of peppermint essential oil on a tissue paper 3 times a day for 5 days, placing it on the collar and breathing naturally for 20 minutes. | Nausea and vomiting | Peppermint oil reduced the frequency of nausea and vomiting, and the discomfort caused by acute nausea. |
| **Efe Ertürk and Taşçı (13)** | Cancer patients undergoing chemotherapy (n=80) | quasi-RCT | Peppermint oil | Application of a drop of aromatic mixture to the area between the upper lip and the nose 3 times a day for 5 days after chemotherapy. | CINV | Peppermint oil significantly reduced the frequency of nausea, vomiting, retching, and the severity of nausea. |
| **Mapp et al. (18)** | Outpatient cancer patients receiving chemotherapy (n=79) | RCT | Peppermint oil | Putting a damp cloth with 2 drops of peppermint oil on the neck area and wait for 30 minutes. | Nausea | The use of peppermint oil reduced the intensity of nausea compared to the control group. |
| **Seale (19)** | Palliative care and hospice patients (n=8) | Quantitative, descriptive study | Peppermint essential oil | Inhalation by adding 1-2 drops of peppermint oil on a cotton swab with medical treatment. | Nausea | The use of peppermint oil in combination with medical treatment reduced the frequency of nausea. |
| **Sriningsih and Lestari (20)** | Cervical cancer patients receiving chemotherapy (n=60) | Semi-experimental study | Ginger essential oil | Adding 5 drops of ginger oil into a mask and inhale for 10 minutes and repeating this application 30 minutes before starting the meal and when the patients feel nauseous. | Nausea and vomiting | The use of ginger oil reduced the incidence of patients experiencing nausea and vomiting. |
| **Lua and Zakaria (21)** | Group of patients with breast cancer receiving chemotherapy (n=75) | Single blind randomized controlled crossover study | Ginger essential oil | Five days of aromatherapy treatment (2 drops at least 3 times a day) using ginger essential oil or ginger placebo | Nausea, vomiting and quality of life | Ginger oil inhalation has the effect of relieving acute nausea and reducing ENT. |
| **Zorba and Ozdemir (33)** | Group of patients with breast cancer receiving chemotherapy (n=75) | quasi-RCT | Aromatic blend of mint (2%), bergamot (1%) and cardamom (1%) | In the 2nd, 3rd and 4th chemotherapy cycles;<br>Inhalation group: smelling 2 mL of aromatic mixture dropped on a cotton ball for 3 minutes before chemotherapy<br>Massage group: 10 minutes of aromatherapy foot massage on each foot | CINV | Applications by massage and inhalation reduced the severity of acute nausea. |
| **Khalili et al. (34)** | Patient group with different cancer types receiving chemotherapy (n=66) | RCT | Cardamom oil | In the intervention group, cardamom oil, and in the placebo group, deep breathing three times a day, 2 times a day through pads impregnated with distilled water. | CINV | Cardamom oil inhalation reduced the severity of nausea in the acute phase. |

**Table 1.** Continued

| Literature | Sample | Research design | Essential oil | Method of application | Symptom | Result |
|---|---|---|---|---|---|---|
| **Santosh et al. (35)** | Patient group with different cancer types receiving chemotherapy (n=60) | Semi-experimental study | Lavender essential oil | Massage with 6 drops of lavender oil and inhalation of lavender oil for 10 minutes, every hour, every hour, before and until the end of chemotherapy. | Anxiety, nausea and vomiting | Aromatherapy application with lavender oil reduced anxiety, nausea and vomiting levels. |
| **Wilkinson et al. (39)** | Patient group with different cancer types (n=103) | RCT | Roman chamomile essential oil | One hour weekly aromatherapy massage for 3 weeks with Roman chamomile oil. | Anxiety, quality of life, physical and psychological symptoms | Massage with Roman chamomile oil reduced anxiety levels, increased the effectiveness of massage and improved physical and psychological symptoms and overall quality of life. |
| **Soden et al. (40)** | Patient group with different cancer types (n=42) | RCT | Lavender essential oil | Massage only for 30 minutes once a week for 4 weeks or aromatherapy massage with lavender essential oil. | Pain, anxiety, sleep and quality of life | The addition of lavender essential oil did not enhance the beneficial effects of massage. However, patients with psychological disorders responded better to treatment. |
| **Pimenta et al. (41)** | Chronic myeloid leukemia (CML) patients (n=42) | RCT | Orange essential oil | Ten mg diazepam administration to the 1st group, 10 mL of citrus essential oil inhalation for 30 minutes to the 2nd group, inhalation of saline solution to the placebo group for 30 minutes. | Anxiety | Aromatherapy application with citrus essential oil reduced anxiety-related signs and symptoms in CML patients. |
| **Imanishi et al. (42)** | Patient group diagnosed with breast cancer (n=12) | Open semi-comparative trial | Aromatic blend of sweet orange oil, lavender oil and sandalwood oil | Massage (8 times in total) using a 30-minute aromatic mixture twice a week for 4 weeks. | Anxiety, depression and immunological parameters | After the 5th and 8th sessions, the anxiety level of the patients decreased and their depression level did not change. Aromatherapy massage has improved the immunological status. |
| **Chang (43)** | Terminal stage cancer patients (n=58) | Pretest-Posttest Control Group model | Blend of bergamot, lavender and frankincense | Five minutes of hand massage for 7 days with an aromatic mixture to the aromatherapy group and a carrier oil to the control group. | Pain, anxiety and depression | Aromatherapy hand massage had a positive effect on pain and depression in terminal cancer patients. |
| **Beyliklioğlu and Arslan (44)** | Patients diagnosed as having breast cancer and planned for breast surgery (n=80) | RCT | Lavender oil | Twenty minutes of inhalation from gauze containing 3-4 drops of lavender oil on the day of surgery. | Anxiety | Aromatherapy with lavender oil reduced anxiety levels. |

**Table 1.** Continued

| Literature | Sample | Research design | Essential oil | Method of application | Symptom | Result |
|---|---|---|---|---|---|---|
| **Ozkaraman et al. (45)** | Patient group with different cancer types (n=70) | RCT | Lavender oil, tea tree oil | Inhalation aromatherapy with 3 drops of lavender oil to one group and 3 drops of tea tree oil to one group every night for 1 month | Anxiety and sleep quality | Lavender oil inhaled every night before sleep reduced anxiety levels and improved sleep quality. Tea tree oil had no effect on state and trait anxiety levels, but improved sleep quality. |
| **Khiewkhern et al. (46)** | Patient group diagnosed as having colorectal cancer (n=66) | Single-blind-RCT | Ginger essential oil | Aromatherapy massage (with ginger and coconut oil) three times a week for 1 week. | Anxiety, depression, fatigue, pain, nausea, vomiting and | Aromatherapy massage with ginger essential oil showed positive effects on fatigue, pain, anxiety and immunological parameters. |
| **Yıldırım et al. (49)** | Cancer patients receiving palliative care (n=68) | RCT | Lavender oil | On the 2nd and 3rd days of the study, 10 deep breaths of 3 mL of 100% pure lavender oil before going to bed in the evening (the oil was left 1 m away from the patient during the night). | Immunological parameters | Lavender oil application increased the sleep quality of the patients, but did not affect their vital signs. |
| **Heydarirad et al. (57)** | Patient group with different cancer types (n=54) | Single-blind-RCT | Rose essential oil | Aromatherapy group inhalation of oil (5% and 10% rose essential oil) for 20 minutes half an hour before bedtime for two weeks. | Sleep quality and vital signs | Inhalation aromatherapy applied with rose essential oil increased the sleep quality of the patients. |
| **Blackburn et al. (58)** | Patients newly diagnosed as having acute leukemia (n=50) | RCT | Lavender oil, peppermint oil, chamomile oil | Inhalation of 8 drops of essential oil or placebo every night for 3 weeks. | Sleep quality | Aromatherapy practice has a positive effect on sleep and has improved symptoms such as fatigue, lethargy, loss of appetite, depression and anxiety. |
| **Hamzeh et al. (59)** | Patient group with different cancer types (n=120) | RCT | Lavender oil, peppermint oil | Aromatherapy groups inhalation for 20 minutes by dripping 3 drops of essential oil on cotton for 7 days. The control group likewise inhaled aromatic distilled water. | Sleep quality | Inhalation aromatherapy with lavender and peppermint essential oils improved the sleep quality of cancer patients. |
| **Kawabata et al. (60)** | Cancer patients receiving palliative care (n=74) | RCT | Lavender oil, orange oil | Aromatherapy massage with essential oils in a single session (30 minutes) at night. | Sleep quality and fatigue | Aromatherapy massage had no positive effect on sleep quality and fatigue. |
| **Yayla and Ozdemir (66)** | Cancer patients planned to receive chemotherapy (n=123) | quasi-RCT | Lavender oil, eucalyptus oil | Inhalation of 3 drops of essential oil for 3 minutes before inserting a needle into the implantable venous port catheter. | Pain and anxiety | Only aromatherapy with lavender essential oil has an effect on pain. It had no effect on anxiety. |

**Table 1.** Continued

| Literature | Sample | Research design | Essential oil | Method of application | Symptom | Result |
|---|---|---|---|---|---|---|
| **İlter et al. (67)** | Patient group with different cancer types (n=60) | Semi-experimental | Blend of orange, chamomile and lavender essential oil (1:1:1) | During the post-catheterization process, inhalation of the aromatic mixture by dripping on the pillow for 15 minutes. | Pain and vital signs | Inhalation aromatherapy reduced the pain experienced during the procedure and had no effect on vital signs and saturation. |
| **Babashahi Kohanestani et al. (68)** | Patients with acute myeloid leukemia (AML) (n=70) | Semi-experimental | Lavender oil | Inhalation of 2 drops of essential oil 1 time per day for 3 days. | Pain | Aromatherapy application with lavender oil reduced the intensity of pain. |
| **Ovayolu et al. (69)** | Patient group diagnosed as having breast cancer (n=280) | RCT | Essential oil blend of lavender, mint, chamomile, jasmine, violet, rosemary and eucalyptus | - Aromatherapy massage group: 3 times a week for 1 month, 35 minutes of aromatherapy massage.<br>- Classic massage group: Massage with olive oil for 35 minutes, 3 times a week for 1 month.<br>- Inhalation group: Inhalation of aromatic mixture for 5 minutes, 3 times a week for 1 month.<br>- Control group: no application. | Quality of life, physical and psychological symptoms | Inhalation aromatherapy and aromatherapy massage increased the quality of life and reduced the physical and psychological symptoms experienced by patients. |

CINV: Chemotherapy-induced nausea and vomiting, RCT: Randomized controlled trial

purposes in palliative care patients. However, there is a need for well-designed randomized controlled clinical studies with a large sample group that evaluate the effect of aromatherapy on symptoms with standard measurement tools.

### Ethics

**Peer-review:** Externally peer reviewed.

### Authorship Contributions

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

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