Original Article

DOI: 10.14235/bas.galenos.2022.63935
Bezmialem Science 2022;10(6):777-85

Identification of Drug-Related Problems and Investigation of Related Factors in Patients with COVID-19: An Observational Study

COVID-19'lu Hastalarda İlaçla İlişkili Sorunların Belirlenmesi ve İlişkili Faktörlerin İncelenmesi: Gözlemsel Bir Çalışma

Muhammed Yunus BEKTAY[1], Mesut SANCAR[2], Fatmanur KARAKÖSE OKYALTIRIK[3], Bülent DURDU[4], Fikret Vehbi İZZETTİN[1]

[1]Bezmialem Vakıf University Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Turkey
[2]Marmara University Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Turkey
[3]Bezmialem Vakıf University Faculty of Medicine, Department of Chest Diseases, İstanbul, Turkey
[4]Bezmialem Vakıf University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

ABSTRACT

Objective: Clinical prognosis of coronavirus disease-19 (COVID-19) may be severe and unexpected. Patients may quickly progress to respiratory failure, infections, multiple organ dysfunction, and sepsis. The main objective of this study is to investigate the drug-related problems of patients with COVID-19 and related factors.

Method: A prospective observational study was conducted on patients with COVID-19 between September 2020 and May 2021. Patients' demographics, comorbid diseases, prescribed medicines and laboratory findings were recorded. Drug-related problems (DRPs) were identified by a clinical pharmacist according to recent guidelines, UpToDate® clinical decision support system and evidence-based medicine.

Results: The median age of 107 patients was 64 and 50.46% of them were male. The median number of comorbidities was 3 (2-4) per patient. The majority of the patients had at least one comorbidity (88.79%) other than COVID-19 and the most frequent comorbidities were hypertension, diabetes mellitus and coronary artery disease. The total number of DRPs was recorded as 201 and at least one DRP was seen in 75 out of 107 patients. The median number of DRPs was 2 (0-8). In multivariate model, number of

ÖZ

Amaç: Koronavirüs hastalığı-19 (COVID-19) ağır ve beklenmedik şekilde seyredebilmektedir. Hastalarda solunum yetmezliği, ikincil enfeksiyonlar, çoklu organ yetmezliği ve sepsis tablosu görülebilmektedir. Bu çalışmanın amacı, COVID-19'lu hastalarda ilaçla ilgili sorunları (İLİS) ve ilişkili faktörleri araştırmaktır.

Yöntemler: Eylül 2020 ile Mayıs 2021 tarihleri arasında COVID-19'lu hastaların katılımıyla prospektif gözlemsel bir çalışma tasarlanmıştır. Hastaların demografik özellikleri, komorbid hastalıkları, kullandıkları ilaçlar ve laboratuvar bulguları kayıt altına alınmıştır. İLİS'lerin belirlenmesi; klinik eczacı tarafından güncel kılavuzlara ve UpToDate® klinik karar destek sistemlerine göre yapılmıştır.

Bulgular: Toplamda 107 hasta çalışmaya dahil edilmiştir. Yaşların medyanı 64 (54,5-76,0) idi ve hastaların %50,46'sı erkek olarak kayıt altına alınmıştır. Komorbiditelerin ortanca sayısı 3 (2-4) idi. Hastaların çoğunluğunda COVID-19 dışında en az bir komorbidite (%88,79) mevcuttu ve en sık görülen komorbiditeler hipertansiyon, diabetes mellitus ve koroner arter hastalığı olarak belirlenmiştir. Toplam İLİS sayısı 201 olarak belirlenmiş ve 107 hastanın 75'inde en az bir İLİS görüldü. Medyan İLİS sayısı 2 (0-8) olarak kaydedilmiştir. Çok değişkenli regresyon modeline göre

Address for Correspondence: Muhammed Yunus BEKTAY, Bezmialem Vakıf University Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Turkey
E-mail: yunusbektay@gmail.com **ORCID ID:** orcid.org/0000-0003-2032-9957

Cite this article as: Bektay MY, Sancar M, Karaköse Okyaltırık F, Durdu B, İzettin FV. Identification of Drug-Related Problems and Investigation of Related Factors in Patients with COVID-19: An Observational Study. Bezmialem Science 2022;10(6):777-85

Received: 29.12.2021
Accepted: 23.02.2022

comorbidities (odss ratio (OR)=1.952; 95% confidence interval (CI)=1.07-3.54, p<0.05, number of medications (OR=1.344; 95% CI=1.12-1.61, p<0.001), and serum potassium levels (OR=5.252; 95% CI=1.57-17.56, p<0.001) were the factors related with DRP.

Conclusion: This study highlights the DRPs and related factors in patients with COVID 19 in hospital settings. Considering unknown features of the infection and multiple medication use, DRPs are likely to occur. It would be beneficial to consider the related factors in order to reduce the number of the DRPs.

Keywords: COVID-19, hospital settings, clinical pharmacist, drug-related problems, pharmaceutical care need

komorbidite sayısı (olasılık oranı (OO)=1,952; %95 güven aralığı (GA)=1,07-3,54, p<0,05), ilaç sayısı (OO=1,344; %95 GA=1,12-1,61, p<0,001) ve serum potasyum seviyeleri (OO=5,252; %95 GA=1,57-17,56, p<0,001) ile ilişkili faktörler olarak belirlenmiştir.

Sonuç: Bu çalışma COVID 19'lu hastalarda İLİS ve ilişkili faktörleri incelemektedir. Enfeksiyonun bilinmeyen özellikleri ve ilaç kullanım ihtiyacı göz önüne alındığında İLİS'lerin ortaya çıkması muhtemeldir. İLİS sayısını azaltmak için ilgili faktörleri göz önünde bulundurmanın faydalı olacağı kanaatindeyiz.

Anahtar Sözcükler: COVID-19, hastane ortamı, klinik eczacı, ilaçla ilgili sorunlar, farmasötik bakım ihtiyacı

Introduction

Coronavirus disease-19 (COVID-19) is a viral infection causing severe acute respiratory syndrome in humans. Suspicion of COVID-19 is firstly reported as pneumonia with unknown etiology on December 31th in China (1). An increase in the number of patients with pneumonia was identified on 31 December 2019 and then it was identified as the new Coronavirus on January 7th, 2020 which was not detected in humans before. After this date, the number of patients including infected health care professionals increased rapidly. The first case with COVID-19 in Turkey was confirmed on March, 11th, 2020 (2,3). Current situation in Turkey on January 13rd, 2022 involved more than 9.4 million confirmed cases and 82,361 deaths. The numbers are increasing each day (3). The rapid global spread of COVID-19 continues, which remains a danger throughout the world however, an accurate and certain treatment is still being investigated by the scientists.

The treatment of COVID-19 is complex and requires different groups of drugs and combinations. However, despite all effort and clinical studies, a conclusive consensus on treatment is still lacking (4). Individualized treatment measures were preferred according to to clinical severity and conditions. In many cases, multiple medication use was inevitable. The most prescribed drugs for the treatment of COVID-19 were antivirals, antibiotics, analgesics and antipyretics, corticosteroids, tocilizumab, anakinra, and convalescent plasma, etc. (4).

Since the concept of pharmaceutical care has emerged, one of the primary services of pharmacists is to ensuring optimal drug use and minimize adverse events occuring as a result of medications (5). The pharmacist-led cognitive services, which are defined as *"the use of specialized knowledge by the pharmacist for the patient or health professionals for the purpose of promoting effective and safe drug therapy"* aims to optimize pharmacotherapy (6).

The pharmacist should evaluate the medication therapies using their skills about pharmacotherapy as their daily routine (7). As an expert on drug use and pharmacotherapy pharmacist has an essential role in identifying and resolving the Drug-Related Problems (DRPs). The term DRPs could be defined as any events or circumstances related to pharmacotherapy that could interfere with the health outcomes (8). According to the definition of the Pharmaceutical Care Network Europe, DRP is *"An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes*" (9). Potential or actual DRPs may be harmful for the patient and increase the healthcare costs (10). In a recent study held by Liew et al. (11), up to 60 % potentially inappropriate prescribing observed in patients above the age of 65 years.

The prevention and resolving of DRPs requires a professional experience and collaboration among the healthcare professionals. The pharmacists are one of the most qualified healthcare professionals to identify and prevent DRPs due to their pharmacotherapy knowledge, and regular communication with patients (5). During the medication review process, DRPs should be identified and classified by a clinical pharmacist. To optimize the drug therapy, an evaluation of the indications, dosage, adherence, adverse events, and therapeutic effects of all drugs should be assessed and recorded (7). Despite increased attention and identification of DRPs, management and prevention of this issue is still a challenge.

Aim of the Study

The main objective of this study is to investigate the pharmaceutical care need of patients with COVID-19 in hospital settings. The primary outcomes of the present study were the identification of DRPs and influencing factors.

Methods

Study Design and Sample Size

A prospective observational was study conducted on patients with COVID-19 who were admitted to pulmonology service at a tertiary-care university hospital in Istanbul, Turkey between September 2020, and May 2021. The patients in need of intensive care were excluded. The patients with COVID-19 indication enrolled in this study were diagnosed according to the World Health Organization and Turkish Ministry of Health Interim Guidance (12). A sample size of 85 was required within a 5% margin of error and confidence intervals (CI) of 95% (13).

Data Collection

The patients' demographic factors (age, gender, body weight etc.), comorbid diseases, prescribed medicine (dosing, frequency, and treatment duration) and duration of hospital stay were recorded. In addition, blood pressure, heart rate, oxygen saturation, respiratory rate, and laboratory findings (e.g., creatinine, uric acid, fasting blood glucose, hemogram, LACE index, Quick COVID-19 severity index, COVID-GRAM Critical Illness Risk Score) on admission were recorded (14-16). Meanwhile, the number of prescribed medicine or over-the-counter medications during hospital stay were collected. The identification of DRPs was made by the clinical pharmacist according to recent guidelines, UpToDate® and Medscape® clinical decision support system, and evidence-based medicine. Potential drug-drug interactions (pDDI) were determined by using UpToDate®. Among detected pDDIs, only X (avoid combination), D (consider therapy modification) and C (monitor therapy) categories were taken into consideration.

All assessments about DRPs which had clinical significance were performed by clinical pharmacists. The DRPs and clinical significance were evaluated using the Hepler and Strand DRPs classification system (17). Data were collected using convenience sampling methods. This study were reported according to recommendation of Strengthening the Reporting of Observational Studies in Epidemiology standards (Figure 1) (18).

Statistical Analysis

Descriptive statistics, mean, median, standard deviation, and interquartile range (IQR) or counts and percentages were given for continuous variables. The frequency, percentage were given for categorical variables. The normality of continuous variables was tested using the Kolmogorov-Smirnov test. The difference among groups was analyzed with an independent t-test or Mann-Whitney U test. Chi-square tests were used to investigate the relationship between categorical variables. The univariate logistic regression analysis was used to determine which variables were significant by using $p<0.20$. The significant variables were included in the binary logistic regression analysis. The missing data were excluded from the analysis. All the data were analyzed by using SPSS version 26® and Jamovi version 1.6.

Ethical Approval

The study protocol was approved by the Ministry of Health and the Local Ethics Committee of Bezmialem Vakıf University's clinical research ethics committee (approval number of 5/42, 06.05.2020). Informed consent was obtained from all individual participants included in the study.

Results

Demographics, Medications, and Drug-Related Problems (DRPs)

The total number of patients were 107, the median (IQR) age of patients was 64 (54.5-76.0) and 50.46% of them were male (Table 1). The median (IQR) score of body mass index was 25.4 (23.7-27.7). The median number of comorbidities (IQR) was 3 (2-4) per patient. The majority of the patients had at least one comorbidity (88.79%) other than COVID-19. The median (IQR) number of medicines prescribed, and the median number of days of hospital stay were 12.8 (8-16) and 9 (6-15) days, respectively (Table 1). The most frequently prescribed medicines were favipiravir, enoxaparin, pantoprazole, paracetamol, and dexamethasone (Figure 2). The total number of DRP was recorded as 201, and at least one DRP was seen in 75 out of 107 patients (Table 2). The baseline vital signs of the patients were given in Table 3. The mean and median (IQR) numbers of DRPs were 1.93±1.91/patient and 2 (0-8), respectively (Table 4). According to our results, 140 of the DRPs consisted of pDDIs. One the most abundant pDDIs was increased bleeding due to concomitant use of dexamethasone and enoxaparin.

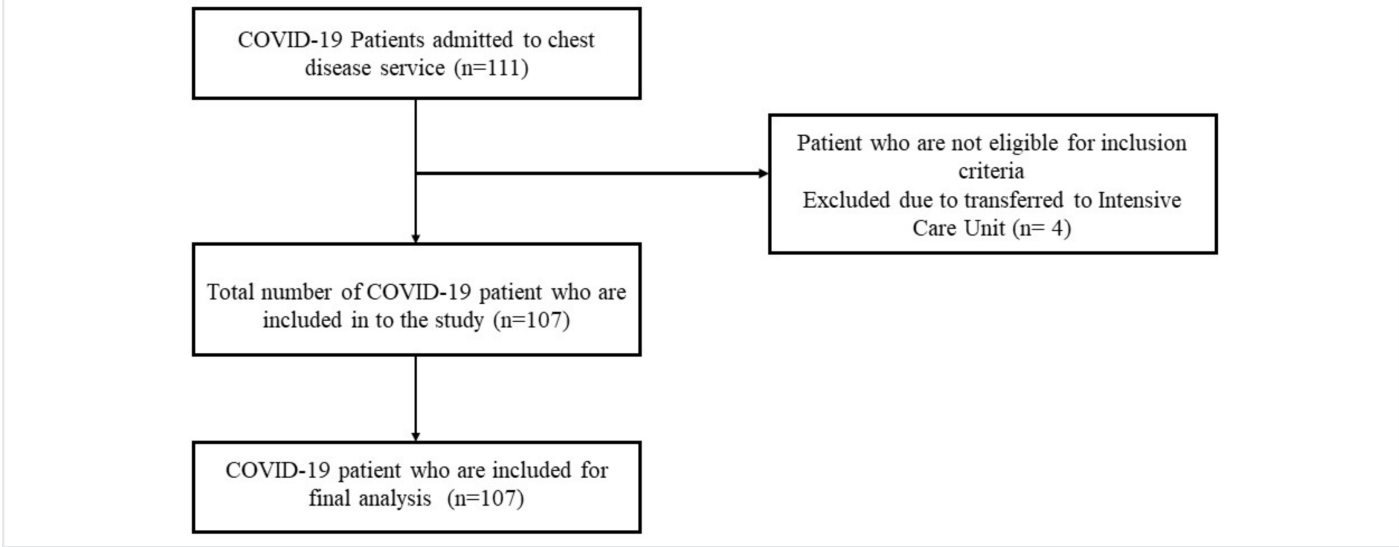

Figure 1. STROBE flow chart

STROBE: Strengthening the reporting of observational studies in epidemiology, COVID-19: Coronavirus disease-2019

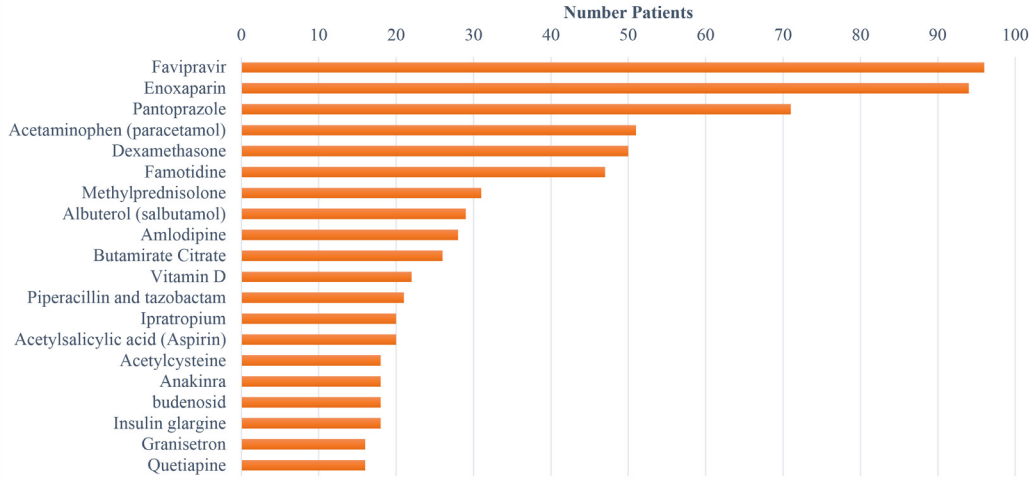

Figure 2. Number of prescribed medications

Medical conditions of the participants are summarized in Table 1. Among 107 patients, nearly half of them were diagnosed with hypertension (HT) (n=54, 50.47%). The second and the third most common comorbidities were Diabetes Mellitus (DM) (n=30, 28.47%) and coronary artery diseases (CAD) (n=25, 23,365), respectively (Table 1). Among 75 patients with detected DRP, 44 patients had HT, 25 patients had DM and 24 patients had CAD (Table 1).

Vital Signs and Biochemical Findings

Baseline clinical and vital findings of the participants were recorded and presented in Table 3 and 4. The median (IQR) of body temperature of patients was recorded as 37 (36.4-37.5). Among our sample, median (IQR) values of heart beats per minute and oxygen saturation (spO_2) were 87 (78-96.5) and 93 (88-95), respectively. The median (IQR) systolic and diastolic blood pressure values were 131 (119-145) and 76 (65-82), respectively. The median (IQR) respiratory rate of the participants was 20/min (16-22). Participants' basal biochemical values are given in Table 4.

Factors associated with the Drug-Related Problems

Univariate analysis exploring the factors associated with DRP are presented in Table 5. The number of comorbidities [odds ratio (OR)=2.097, 95% confidence interval (CI)=1.43-3.08; p<0.001)], number of medications (OR=1.32, 95% CI=1.17-1.49; p<0.001), serum urea mg/dL levels (OR=1.035, 95% CI=1.01-1.06; p<0.05), serum blood urea nitrogen levels (OR=1.00, 95% CI=1.00-1.00; p<0.05), serum potassium levels (OR=2.409, 95% CI=1.16-5.00; p<0.05), serum lymphocyte ratio (OR=0.967, 95% CI=0.936-1.00; p<0.05), Quick COVID severity index score (OR=1.23, 95% CI=1.01-1.353; p<0.05), and LACE index score (OR=1.23, 95% CI=1.07-1.42; p<0.001) were associated with the DRPs. Binary logistic regression analysis for DRPs is presented in Table 5.

A binomial logistic regression was performed to ascertain the effects of the number of medications, the number of comorbidities, BUN, serum potassium levels, lymphocytes ratio, LACE index, score, Quick COVID severity Index, serum urea level, on the likelihood that participants had a DRP. The logistic regression model was statistically significant, $\chi^2(8)=57.842$, p<0.0001. The model explained 59.7% (Nagelkerke R^2) of the variance in DRPs and correctly classified 84.1% of cases. Sensitivity was 92.1%, specificity was 64.52%, positive predictive value was 61.5% and negative predictive value was 74.3%. Of the 8 predictor variables, only 4 were statistically significant: number of comorbidities, number of medications, serum potassium levels and lymphocyte ratio (Table 5). Increased number of comorbidities (OR=1.952; 95% CI=1.07-3.54, p<0.05), number of medications (OR=1.344; 95% CI=1.12-1.61, p<0.001), and serum potassium levels (OR=5.252; 95% CI=1.57-17.56, p<0.001) were associated with an increased likelihood of exhibiting DRP. But, increasing lymphocyte ratio (OR=0.953; 95% CI=0.91-0.99, p<0.05) was associated with a reduction in the likelihood of exhibiting DRPs.

Discussion

In this study, we investigated the DPRs in patients with COVID-19 and related factors in hospital settings. Hospitalized patients with COVID-19 have multiple comorbidities and need multiple medications (4). Currently, many scientists are investigating alternative medicine for COVID-19. However, there is no exact treatment alternative for COVID-19 approved by different authorities. On the other hand, the ethical aspects of these options are still questionable (19).

In this study, many of the participants were prescribed with antivirals, antibiotics, analgesics, antipyretics, and anti-thrombotic drugs. Based on the primary findings, the number of comorbidities, serum potassium levels, lymphocyte ratio, and the number of medications were associated with the number of DRPs. The identified risk factors should be assessed by pharmacist to prevent DRPs in patients with COVID-19.

According to Pradhan and Olsson (20) and Imam et al. (21), HT and DM were the most common comorbid diseases among patients with COVID-19. Another study held in Turkey

Table 1. Patient characteristics

Total number of patients	Total n=107	DRP present (n=75)	DRP not present (n=32)	p
Gender n (%)				N.S
Female	53 (49.53%)	38 (35.51%)	15 (14.02%)	
Male	54 (50.46%)	37(34.58%)	17(15.88%)	
BMI [median (IQR)]	25.4 (23.7-27.7)	24.9 (23.7-28.2)	25.9 (23.7-27.4)	*N.S*
Weight (kg)	75 (15, 65.0-80.0)	72 (65-80)	75 (70-80)	
Height (m)	1.66 (0.135, 1.62-1.75)	1.65 (1.60-1.75)	1.68 (1.65-1.75)	
Age [median (IQR)]	64 (54.5-76.0)	68 (58-76.0)	60 (50.5-67.0)	***p<0.05***
No. of comorbidities [median (IQR)]	3 (2-4)	4 (2-5)	2 (1.75-3)	***p<0.001***
1 (n, %)	12 (11.21%)	4 (5.33%)	8 (5.33%)	
2 (n, %)	29 (27.10%)	19 (25.3%)	10 (31.25%)	
3 (n, %)	20 (18.69%)	11 (14.6%)	9 (28.12%)	
4 (n, %)	25 (23.36%)	22 (29.3%)	3 (9.37%)	
5 (n, %)	13(12.14%)	12 (16.0%)	1 (3.12%)	
6 (n, %)	8 (7.47%)	8 (10.6%)	0 (0%)	
Comorbidities				NA
COVID-19	107 (100%)	75 (100%)	32 (100%)	
Hypertension	54 (50.47%)	44 (58.6%)	10 (31.25%)	
Diabetes mellitus	30 (28.04%)	25 (33.3%)	5 (15.6%)	
Coronary artery disease	25 (23.36%)	24 (32.0%)	1 (3.12%)	
Cancer	23 (21.50%)	23 (30.6%)	7 (21.87%)	
Chronic obstructive lung disease	20 (18.70%)	18 (24.0%)	2 (6.25%)	
Cerebrovascular disease	11 (10.28%)	10 (13.3%)	1 (3.12%)	
Chronic kidney disease	8 (7.47%)	7 (9.33%)	1 (3.12%)	
Neurological diseases	8 (7.47%)	7 (9.33%)	1 (3.12%)	
Psychiatric diseases	7 (7.65%)	7 (9.33%)	0 (0%)	
Others	32 (29.90%)	20 (26.6%)	12 (37.5%)	
Hospital stay in days [median, (IQR)]	9 (6-15)	10 (6-17.5)	7 (5-11)	***p<0.001***
Number of medication [median, (IQR)]	12.8 (8-16)	14 (10.5-19)	7 (5-10)	***p<0.001***
Quick COVID severity index	2 (0-5)	2 (0-5.5)	0 (0-2)	***p<0.001***
COVID GRAM critical index	140 (117-164)	144 (127-164)	125 (108-164)	***p<0.001***
Charlson comorbidity index	4 (0-5)	4 (2-6)	2 (1-4)	***p<0.001***
LACE index	13 (10-16)	14 (12-16)	10.5 (9-13.3)	***p<0.05***

DRP: Drug related problem, BMI: Body mass index, IQR: Interquartile range

pointed out that DM, HT, and CAD were the most frequent comorbidities among patients with COVID-19 (22). Our findings showed a correlation with their statements. The most common comorbid disease was recorded as HT (50.47%), which was followed by DM (28.04%), and CAD (23.36%) (Table 1). Therefore, detailed medical history should be taken and preventive measures for DRPs should be underlined by the clinical pharmacist.

A retrospective cohort study held by Imam et al. (21) pointed out that older age and increased number of comorbidities were associated with mortality. Older age (>60 years) (OR=3.66, 95% CI=2.57-5.20) and increased number of comorbidities (>3) (OR=4.11, 95% CI=3.00-5.62) were independent predictors of mortality (21). Similarly, our investigation pointed out that increased number of comorbidities (OR=1.952; 95% CI=1.07-3.54, p<0.05) were associated with the increased number of the DRPs. However, in terms of age, there was not statistically difference between the groups (Table 5). Many patients, especially elders, have multiple comorbidities. Knowledge of pharmacist should be implemented into practice to improve healthcare services for patients with COVID-19. A detailed medication review process might be useful to detect and prevent

Table 2. Features drug related problems in patients with COVID-19

	Total	Median	(Min-max)
Total no of DRP	201	2	(0-8)
Drug interactions	140	1	(1-7)
Improper drug selection	40	1	(1-3)
Overdosage	21	1	(1-4)
Untreated indications	-	-	
Adverse reactions	-	-	
Failure to receive drugs	-	-	
Subtherapeutic dosage	-	-	
Drug use without indication		-	

DRP: Drug related problem, COVID-19: Coronavirus disease-2019, Min: Minimum, max: Maximum

Table 3. Baseline vital signs of patients

n=107	Median	(IQR 25-75)
Body temperature, °C	37	(36.4-37.5)
Heartbeat (HBM)	87	(78-96.5)
Oxygen saturation (SpO_2)	93	(88-95)
Systolic blood pressure (mmHg)	131	(119-145)
Diastolic blood pressure (mmHg)	76	(65-82)
Respiratory rate (BPM)	20	(16-22)

HPM: Heartbeat per minute, BPM: Breath per minute, IQR: Interquartile range

Table 4. Baseline biochemical values of participants

n=107	Reference range	Median	(IQR, 25-75)
Acute phase reactants			
CRP mg/dL	*0-5*	63	(97.3, 24.7-122)
Procalcitonin ng/mL	*0-0.5*	0.157	(0.318, 0.02-0.34)
Ferritin ng/mL	*21-274*	369	(649, 142-791)
D-dimer ng/mL	*0-300*	253	(391, 187-578)
Albumin g/dL	*3.2-4.6*	3.60	(0.50, 3.30-3.80)
Renal function parameters			
Urea (mg/dL)	*17-49*	41	(32.5,28.5-61)
Blood urea nitrogen, BUN (mg/dL)	*8-23*	19.2	(15.2, 13.3-28.5)
Creatinine (mg/dL)	*0.7-1.3*	0.88	(0.46, 0.74-1.15)
GFR (mL/min/1.73)	*>90*	78	(36, 60-96)
Hepatic function parameter			
Lactate dehydrogenase, LDH (U/L)	*125-220*	316	(169, 260-429)
Aspartate aminotransferase, AST (U/L)	*5-34*	29	(19.5, 24-43.6)
Alanine aminotransferase, ALT (U/L)	*0-55*	24	(24.5, 14.5-39)
Alkalen phosphatase ALP (U/L)	*40-150*	55	(36.5, 39.3-75.8)
Gamma-glutamyl transferase, GGT (U/L)	*12-64*	31.5	(18.3, 24-42.3)
Total bilirubin (mg/dL)	*0.3-1.2*	0.48	(0.31, 0.31-0.62)
Direct bilirubin (mg/dL)	*0-0.5*	0.23	(0.15, 0.15-0.30)
Amylase (U/L)	*28-100*	36	(31.2, 30-60)
Lipase (U/L)	*8-78*	25	(17.5, 19-36.5)
Electrolytes			
Sodium mmol/L	*135-145*	137	(5, 135-140)
Potassium mmol/L	*3.5-5.1*	4.25	(0.795, 3.89-4.69)
Calcium mg/dL	*8.4-10.6*	8.60	(0.6, 8.3-8.9)
Complete blood count			
White blood cells, WBC (10^3/uL)	*4.5-11*	7.10	(5.69, 5.22-10.9)
Lymphocytes %	*10-50*	16.3	(16.3, 10.3-26.6)
Neutrophiles %	*45-78*	74.3	(16.3, 61.4-82.4)
Monocytes %	*0-12*	6.59	(4.91. 4.52-9.43)
Hemoglobulin (g/dL)	*14.1-17.5*	12.3	(4.52, 10.9-13.7)
Hematocrit %	*40-52*	36.6	(7.44, 32.6-40.1)
Mean corpuscular volume, MCV (fL)	*80-97*	85.6	(7.22, 82.4-89.6)
Prothrombin time, PT (s)	*11.4-16.2*	14.5	(2.10, 13.7-158)
Activated partial thromboplastin time, aPTT (s)	*22-40*	35.1	(7.25, 31.9-39.2)
International normalized ratio, INR	*0.8-1.2*	1.07	(0.215, 0.98-1.1)9

Table 5. Statistical analysis of factors associated with the number of drug-related problems

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI for odds ratio	p value	OR	95% CI for odds ratio	p value
Age, years	1.023	(0.99-1.05)	0.124			
Gender						
Male	0.88	(0.46-2.46)	0.880			
Female	Reference					
Hospital stay (days)	1.051	(0.99-1.12)	0.113			
LDH U/L	1.00	(0.99-1.00)	0.889			
CRP mg/L	0.990	(099-1.00)	0.439			
Procalcitonin ng/mL	1.150	(0.71-1.77)	0.629			
Ferritin ng/mL	1.000	(1.00-1.00)	0.508			
D-Dimer ng/mL	1.000	(1.00-1.00)	0.881			
No of comorbidities	2.097	(1.43-3.08)	**<0.0001**	1.952	(1.07-3.54)	**0.028**
No of medication	1.32	(1.17-1.49)	**<0.0001**	1.344	(1.12-1.61)	**0.001**
Urea mg/dL	1.035	(1.01-1.06)	**0.006**	0.001	(0.00-10.34)	0.129
BUN mg/dL	1.000	(1.00-1.00)	**0.006**	1.000	(1.00-1.00)	0.128
Creatine mg/dL	2.225	(0.71-7.02)	0.172			
Sodium mmol/L	1.066	(0.96-1.18)	0.215			
Potassium mmol/L	2.409	(1.16-5.00)	**0.018**	5.252	(1.57-17.56)	**0.007**
WBC 10^3/µL	0.985	(0.945-1.028)	0.486			
Lymphocyte %	0.967	(0.94-1.00)	**0.050**	0.953	(0.91-0.99)	**0.041**
Quick COVID severity index	1.169	(1.01-1.35)	**0.037**	1.245	(0.98-1.58)	0.070
LACE index	1.233	(1.07-1.42)	**0.003**	0.798	(0.61-1.04)	0.093

OR: Odds ratio, CI: Confidence interval, LDH: Lactate dehydrogenase, CRP: C-reactive protein, BUN: Blood urea nitrogen, WBC: White blood cell, COVID: Coronavirus disease

DRPs. Hence, clinical pharmacists could provide pharmaceutical care for patients with COVID-19 in the hospital setting (7,23).

Previous studies held in either in community pharmacy settings or hospital setting detected different number of DRPs per patient (7,24,25). In our study, the mean number of DRP per patient was recorded as 1.93±1.91/patient. Our results were similar with the studies by Stafford et al. (24) and Rhalimi et al. (25) study. On the other hand, Wang et al. (7) recorded higher number of DRPs per patients than our findings. This difference could be explained by the settings of different studies. For instance, the study by Stafford et al. (24) and our data were obtained from hospital settings. However, the studies by Wang et al. (7) and Rahlimi et al. (25) were conducted in a community pharmacy settings.

Multivariate analysis showed that the number of medication used was associated as independent risk factor for the number of DRPs, which was consistent with previous studies (7,26-28). Polypharmacy is a strong risk factor for DRPs. As a result, the number of used medications increased number of DRPs increased simultaneously. The presented finding extended the understanding that a higher number of medications was also an important predictor of DRP in patients with COVID-19 (OR=1.344; 95% CI=1.12-1.61, p<0.001), that was not studied extensively in the literature before (27,28). Multiple medication use is inevitable with comorbidities. However, many of the DRPs may be prevented with well-planned pharmaceutical care services.

Another significant finding of our study was that serum potassium level was associated with DRPs. Compromised kidney functions are directly related with potassium levels. Many of our participants suffered from HT and DM both of which might compromise the kidney functions. Patient with kidney diseases is more prone to drug related problems (29,30). On the other hand, one of the most used antihypertensive drugs is diuretics which can either spare potassium or prevent potassium secretion in kidneys. Also, hypokalemia or hyperkalemia may be directly related with the pharmacokinetic parameters of drugs. As in our findings, the level of serum potassium was related with DRPs which was consistent with literature (29,30). Pharmacists should take into consideration that fluctuation of serum potassium level may result as adverse events.

Study Limitations

This study had some limitations such as the generalizability of the results was limited as the sample was taken from only one center. Future multicentered studies with larger sample size are required to investigate the pharmaceutical care needs of patients with COVID-19. The sample size was rather small. Finally, the

lack of a control group was a limitation of the present study, which was worth noting.

Conclusion

To the best of our knowledge, presented study was the first to investigate the incidence, type, and related factors of DRPs detected by clinical pharmacists in patients with COVID-19 in hospital settings. This study showed that a considerable proportion of patients had DRPs and the most common category was the potential drug-drug interactions. In the multivariate model, the number of medications, number of comorbidities, serum potassium levels and lymphocytes ratio were the significant related factors with the number of DRPs.

COVID-19 pandemic is still an important healthcare problem all around the world. Pharmacists and pharmacist-led cognitive services will detect, prevent, and decrease unfavorable drug-related events. To improve healthcare services, pharmacists should take responsibility and should become an indispensable component of the COVID-19 healthcare team.

Acknowledgement

The authors of this study are grateful to Bezmialem Vakif University. We are also grateful to Hümeyra Şahin-Bektay for her valuable contribution to our research. The presented study was conducted within the scope of the thesis of a Clinical Pharmacy PhD Program at the Institute of Health Sciences of Marmara University. This study was not funded by any organizations.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ministry of Health and the Local Ethics Committee of Bezmialem Vakıf University's clinical research ethics committee (approval number of 5/42, 06.05.2020).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.Y.B., M.S., F.V.İ., Design: M.Y.B., M.S., F.V.İ., Data Collection or Processing: M.Y.B., M.S., Analysis or Interpretation: M.Y.B., M.S., Literature Search: M.Y.B., F.K.O., B.D., Writing: M.Y.B., M.S., F.K.O., B.D., F.V.İ.

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

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

References

1. World Health Organisation W. Coronavirus disease (COVID-19) Pandemic [Internet]. 2020. 2020 [cited 2020 Jun 10]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. T.C. Sağlık Bakanlığı. COVID-19 (SARS-CoV-2 ENFEKSİYONU) REHBERİ [Internet]. 2020 [cited 2020 Jun 10]. p. 96. Available from: https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf
3. Turkish Ministry of Health. Novel Coronavirus Disease (COVID-19). [Internet]. 2022. Available from: https://covid19bilgi.saglik.gov.tr/tr/
4. Kim MS, An MH, Kim WJ, Hwang T-H. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. PLoS Med 2020;17:e1003501.
5. Costa FA da, Alvarez-Risco JWF van M· A. The Pharmacist Guide to Implementing Pharmaceutical Care. 1st ed. Costa FA da, Alvarez-Risco JWF van M A, editors. Cham, Switzerland; 2020.
6. Cipolee RJ, Strand LM MP. Pharmaceutical care practice. The Patient-Centered Approach to Medication Management. New York, USA: Pharmaceutical care practice. New York, McGraw-Hill Companies; 1998.
7. Wang X, Yang J, Yu X, Wang Z, Wang H, Liu L. Characterization of drug-related problems and associated factors in ambulatory patients in China. J Clin Pharm Ther 2020;45:1058-65.
8. Krähenbühl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf 007;30:379-407.
9. Europe PCN. Pharmaceutical Care Network Europe [Internet]. 2020 [cited 2021 Oct 4]. Available from: https://www.pcne.org/working-groups/2/drug-related-problem-classification
10. Moriarty F, Bennett K, Cahir C, Kenny RA, Fahey T. Potentially inappropriate prescribing according to STOPP and START and adverse outcomes in community-dwelling older people: a prospective cohort study. Br J Clin Pharmacol 2016;82:849-57.
11. Liew TM, Lee CS, Goh SKL, Chang ZY. The prevalence and impact of potentially inappropriate prescribing among older persons in primary care settings: multilevel meta-analysis. Age Ageing 2020;49:570-9.
12. T.C. Sağlık Bakanlığı Bilimsel Danışma Kurulu Çalışması. COVID-19 Salgın Yönetimi ve Çalışma Rehberi [In Turkish] [Internet]. 2022. p. 470. Available from: https://covid19.saglik.gov.tr/Eklenti/41415/0/covid19-toplumdasalginyonetimirehberipdf.pdf
13. AlAteeq DA, Aljhani S, Althiyabi I, Majzoub S. Mental health among healthcare providers during coronavirus disease (COVID-19) outbreak in Saudi Arabia. J Infect Public Health 2020;13:1432-7.
14. van Walraven C, Dhalla IA, Bell C, Etchells E, Stiell IG, Zarnke K, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. CMAJ 2010;182:551-7. doi:10.1503/cmaj.091117
15. Haimovich AD, Ravindra NG, Stoytchev S, Young HP, Wilson FP, van Dijk D, et al. Development and Validation of the Quick COVID-19 Severity Index: A Prognostic Tool for Early Clinical Decompensation. Ann Emerg Med 2020;76:442-53.
16. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med 2020;180:1081-9.
17. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm 1990;47:533-43.
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344-9.

19. Özdinç A, Bildik Ö. Ethical Issues Regarding Investigational Drugs for the Treatment and Prevention of Covid-19. J Br Islam Med Assoc 2021;9:1-13.

20. Pradhan A, Olsson P-E. Sex differences in severity and mortality from COVID-19: are males more vulnerable? Biol Sex Differ 2020;11:53.

21. Imam Z, Odish F, Gill I, O'Connor D, Armstrong J, Vanood A, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med 2020;288:469-76.

22. Az A, Sogut O, Akdemir T, Ergenc H, Dogan Y, Cakirca M. Impacts of Demographic and Clinical Characteristics on Disease Severity and Mortality in Patients with Confirmed COVID-19. Int J Gen Med 2021;14:2989-3000.

23. Hsu W-T, Shen L-J, Lee C-M. Drug-related problems vary with medication category and treatment duration in Taiwanese heart failure outpatients receiving case management. J Formos Med Assoc 2016;115:335-42.

24. Stafford AC, Tenni PC, Peterson GM, Jackson SL, Hejlesen A, Villesen C, et al. Drug-related problems identified in medication reviews by Australian pharmacists. Pharm World Sci 2009;31:216-23.

25. Rhalimi M, Rauss A, Housieaux E. Drug-related problems identified during geriatric medication review in the community pharmacy. Int J Clin Pharm 2018;40:109-18.

26. Stegemann S, Ecker F, Maio M, Kraahs P, Wohlfart R, Breitkreutz J, et al. Geriatric drug therapy: neglecting the inevitable majority. Ageing Res Rev 2010;9:384-98.

27. Chan D-C, Chen J-H, Wen C-J, Chiu L-S, Wu S-C. Effectiveness of the medication safety review clinics for older adults prescribed multiple medications. J Formos Med Assoc 2014;113:106-13.

28. Chan D-C, Chen J-H, Kuo H-K, We C-J, Lu I-S, Chiu L-S, et al. Drug-related problems (DRPs) identified from geriatric medication safety review clinics. Arch Gerontol Geriatr 2012;54:168-74.

29. Kim AJ, Lee H, Shin E-J, Cho E-J, Cho YS, Lee H, et al. Pharmacist-Led Collaborative Medication Management for the Elderly with Chronic Kidney Disease and Polypharmacy. Int J Environ Res Public Health 2021;18:4370.

30. Stemer G, Lemmens-Gruber R. Clinical pharmacy activities in chronic kidney disease and end-stage renal disease patients: a systematic literature review. BMC Nephrol 2011;12:35.