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ORIGINAL ARTICLE

Clinical Pharmacist-Led Medication Review in Hospitalized Confirmed or Probable Patients with COVID-19 During the First Wave of COVID-19 Pandemic

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ABSTRACT

Objectives: Drug-related problems (DRPs) result in serious problems among hospitalized patients, high rates of morbidity and mortality, and increased healthcare costs. This study aimed to identify DRPs by clinical pharmacist-led medication review in hospitalized probable patients with coronavirus disease-2019 (COVID-19) during the first wave of the COVID-19 pandemic.

Materials and Methods: This retrospective cross-sectional study was conducted at the COVID-19 inpatient services of a tertiary university hospital in Türkiye for 3 months (between March 2020 and June 2020) and included hospitalized confirmed or probable COVID-19 patients. The World Health Organization and Turkish Ministry of Health Guidelines case definitions were used to define confirmed and probable COVID-19 patients. Six clinical pharmacy residents provided medication review services during their education and training. DRPs were classified based on the Pharmaceutical Care Network Europe V9.00. The physician's acceptance rate of clinical pharmacists' recommendations was assessed.

Results: Among 202 hospitalized patients with probable or confirmed COVID-19, 132 (65.3%) had at least one drug-related problem. Two hundred and sixty-four DRPs were identified. Drug selection (85.6%) and dose selection (9.2%) were the most common causes of these problems. Among the 80 clinical pharmacist interventions, 48.8% were accepted by the physicians.

Conclusion: Clinical pharmacists identified a significant number of DRPs during the COVID-19 pandemic, particularly those related to drug interactions and drug safety, such as adverse drug reactions. This study highlights the importance of detecting and responding to DRPs in the COVID-19 pandemic.

Keywords: COVID-19, medication review, clinical pharmacist, drug-related problem, PCNE

INTRODUCTION

The first case infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan (China) in December 2019 and spread worldwide, causing a coronavirus disease-2019 (COVID-19) pandemic.[1] Since the pandemic began, 346 million COVID-19 cases have been reported globally, with a total of 5.5 million deaths.[2] Although many vaccination options are available, and many countries have vaccinated a significant number of their people, the COVID-19 pandemic continues to be a major public health problem.[3]

Several clinical trials have continued to evaluate the efficacy and safety of specific drugs in COVID-19 patients.[4] Repurposed

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drugs for COVID-19 are given to treat patients at home, leading to adverse drug events or drug-drug interactions.[5] During the COVID-19 pandemic, clinical pharmacists continue to provide services such as medication review, medication reconciliation, patient education and counseling, and therapeutic drug monitoring in hospitalized patients with COVID-19.[6-7]

Pharmaceutical Care Network Europe (PCNE) defines the medication review as "a structured evaluation of a patient's medicines with the aim of optimizing medicines use and improving health outcomes".[8] Pharmacists play an essential role in medication review, detecting, and resolving drug-related problems (DRPs) on the level of patients and/or healthcare professionals.[9] DRPs are associated with medication errors, adverse drug events, and adverse drug reactions (ADRs).[10-11] Age, sex, presence of comorbidities, the number of drugs, and length of hospital stay are related factors for DRP.[10] Medication review services have also been provided for COVID-19 patients by clinical pharmacists.[1]

Postgraduate education programs in clinical pharmacy (M.Sc. and Ph.D.) has been maintained in Türkiye since 1991. A clinical pharmacist specialist education and training program was initiated by the Republic of Türkiye Ministry of Health in 2018. However, clinical pharmacy services are not yet included as essential requirements at hospitals in Türkiye.

To the best of our knowledge, this is one of the first studies determining DRPs in patients admitted to COVID-19 inpatient services during the first wave of the COVID-19 pandemic in Türkiye. This study aimed to identify DRPs by clinical pharmacist-led medication review in patients admitted to COVID-19 inpatient services during the first wave of the COVID-19 pandemic and evaluate the physicians' acceptance rate of the pharmacist's recommendation.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted in COVID-19 inpatient services, including infectious diseases, pulmonary medicine, and internal medicine wards of a tertiary university hospital in İstanbul, Türkiye, for three months (between March 2020 and June 2020). All patients (> 18 years old) hospitalized for confirmed or probable COVID-19, who stayed at the hospital for more than 24 hours, used at least one drug during their hospitalization, and received the clinical pharmacist-led medication review service during their hospitalization were included. Patients transferred to the intensive care unit during the first 24 hours of hospitalization were excluded from the study. Our study was conducted in 4 clinics; the total number of beds was 60 and 8 doctors, 2 doctors in each clinic, worked. Three clinical pharmacists worked in the clinics alternately, while 3 clinical pharmacists supported the study remotely. The study protocol was approved by the local Clinical Research Ethical Committee of the Marmara University Faculty of Medicine (approval number: 09.2020.668, date: 12.06.2020).

Six clinical pharmacy residents provided medication review services during their education and training at Marmara University during the COVID-19 pandemic. DRPs were evaluated and recorded by at least two different clinical pharmacists based on electronic hospital records and clinical pharmacist notes. Drug-related problems detected by the clinical pharmacist were verbally reported to the physician.

The patient's demographic (including age and sex), clinical (including comorbidities), and laboratory data (including complete blood count, lactate dehydrogenase, creatinine, coagulation tests, procalcitonin, C-reactive protein), the result of real-time reverse transcriptase-polymerase chain reaction (PCR) test from nasopharyngeal specimens were anonymously recorded to the patient follow-up and evaluation form. Biochemical data were recorded on the first day of hospitalization. In all patients, the Charlson comorbidity index was calculated.[12]

The World Health Organization (WHO) and Republic of Türkiye Ministry of Health Guideline case definitions were used to define confirmed and probable COVID-19 patient.[13,14] The Turkish Ministry of Health guide defined a confirmed case as "among the cases that meet the definition of a probable case, cases with SARS-CoV-2 detected by molecular methods". Those who have clinical findings and/or contacts with patients diagnosed with COVID-19 are defined as "probable cases".[14]

Clinical pharmacist residents assessed all medication orders of hospitalized patients with confirmed and probable COVID-19. Potential drug-drug interactions were evaluated using Lexicomp® Drug Interactions (Wolters Kluwer Health Inc., 2020), Micromedex® Drug Information, and Drug Interactions (Truven Health Analytics Inc., 2020). International guidelines in UpToDate Drug Information and Micromedex Drug Information and the national guideline of COVID-19 for adult patients published by the Turkish Ministry of Health were used to evaluate the appropriateness of drugs. Drug-related problems were classified using the PCNE V9.00-Turkish Version.[15] PCNE, one of the most widely used classification systems, was used to classify DRP in hospital practice.[9,16] PCNE has been translated into various languages in countries where clinical pharmacy is practiced[15,17] and consists of five parts: problem, cause, intervention, intervention acceptance, and status. The "status of DRP" could not be evaluated in PCNE because the study was retrospective. The type and reason for all drug-related problems, the rate of clinical pharmacists' recommendations, and the physician's acceptance rate of clinical pharmacists' recommendations were assessed.

Statistical analysis

Sample size not calculated. Descriptive variables were represented as mean [standard deviation (SD)] and/or median [interquartile range (IQR)] for continuous variables and number (%) for ordinal and nominal variables. Based on the findings of the Kolmogorov-Smirnov test, Mann-Whitney U test was used to compare the two groups. Categorized data were analyzed using the chi-square or Fisher exact tests. $p < 0.05$ was considered significant. Spearman's rank analysis was used to determine the correlation between continuous variables.

RESULTS

The study included 202 hospitalized patients with COVID-19. The PCR test results of 195 of them were identified as 112 confirmed cases and 83 probable cases. The mean age was 59.2 ± 19.3 years, with 52% females. The median (IQR) number of drugs taken *per* patient was 6.0 (4.0-8.0), and polypharmacy (patients receiving more than five drugs concomitantly) was observed in 62.9%. Among these patients, the median (IQR) hospital stay was 7.0 (4.0-11.0) days. The majority of patients had more than three comorbidities (49%), and 1260 drugs were evaluated in this study. The most commonly used drugs were hydroxychloroquine 87.1%, enoxaparin 70.3%, azithromycin 28.2%, and favipiravir 26.2% (176/202, 142/202, 57/202, and 53/202, respectively). The number of patients with two or more DRPs was 74 (36.6%). Patients with DRP had a higher total number of drugs than patients without DRP ($p < 0.05$). Table 1 summarizes the differences between the variables and the main causes of DRPs. There was a positive moderate correlation between the number of DRPs and the total number of drugs and a positive weak correlation between the Charlson comorbidity index [r= 0.317 and r= 0.214, respectively, ($p < 0.01$)]. In Table 2, there was no significant difference in

Table 1. Patients' characteristics (n= 202)

Characteristics	Total patients (n= 202) n (%)	Patients with DRP (n= 132) n (%)	Patients without DRP (n= 70) n (%)	p
Sex				
Male	97 (48.0)	62 (47.0)	35 (50.0)	NS
Female	105 (52.0)	70 (53.0)	35 (50.0)	
Age				
Median	59.0 (18.3)	58.8 (1.6)	60.1 (2.1)	
Older patients (≥ 65 years old)	78 (38.6)	51 (38.6)	27 (38.6)	NS
Charlson comorbidity index				
Median (IQR)	2.0 (1.0-4.0)	3.0 (1.0-4.0)	2.0 (1.0-4.0)	NS
Total number of medications				
Median (IQR)	6.0 (4.0-8.0)	6.0 (4.0-8.8)	5.0 (3.0-7.0)	< 0.01
Classification based on total number of medications				
< 5	76 (37.6)	45 (34.1)	31 (44.3)	NS
≥ 5	126 (62.4)	87 (65.9)	39 (55.7)	
Duration of hospitalization (day)				
Median (IQR)	7.0 (4.0-11.0)	7.0 (4.0-11.0)	7.0 (5.0-14.5)	NS
Result of SARS-CoV-2 RT-PCR				
Positive	112 (55.4)	72 (54.6)	40 (57.2)	NS
Negative	83 (41.1)	54 (40.9)	29 (41.4)	
Unknown/missing data	7 (3.5)	6 (4.5)	1 (1.4)	
Number of patients who received COVID-19 treatment				
Yes	182 (90.1)	118 (89.4)	64 (91.4)	NS
No	20 (9.9)	14 (10.6)	6 (8.6)	
The most commonly used medication in the management of COVID-19				
Hydroxychloroquine	176 (87.1)	115 (87.1)	60 (85.7)	NS
Enoxaparin	142 (70.3)	93 (70.5)	49 (70.0)	NS
Azithromycin	57 (28.2)	42 (31.8)	15 (21.4)	NS
Favipiravir	53 (26.2)	30 (22.7)	23 (32.9)	NS
Oseltamivir	7 (3.5)	4 (3.0)	3 (4.3)	NS
Tocilizumab	5 (2.5)	1 (0.8)	4 (5.7)	NS

IQR: Interquartile range, DRP: Drug-related problem, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, RT-PCR: Reverse transcriptase-polymerase chain reaction, NS: No significant

biochemical parameters between patients with and without DRPs ($p > 0.05$).

The median number of DRPs/patients was 1.3. In Table 3, the incidence of DRPs was "treatment effectiveness" (55 of 264 DRPs; 20.8%), followed by "treatment safety" (140 of 264 DRPs; 53.0%). Within the "treatment effectiveness" category, "untreated symptoms or indication" was the dominant category (46 of 140; 32.9%). A total of 270 DRP causes were identified (Table 3). "Drug selection" category was the primary cause of DRPs (231 of 270; 85.6%), followed by "drug dose" (25 of 270; 9.3%). Among drug selection problems, the most common DRPs were "inappropriate combination of drugs or drugs and herbal medication", "no indication for drug" and "no drug treatment despite existing indication" (108 of 231, 46.8%; 54 of 231, 23.4% and 47 of 231, 20.3%; respectively). The combination of azithromycin and hydroxychloroquine constitutes 52.8% of drug-drug interactions. Of the 112 planned interventions, 91.1% were at the prescriber level. According to the PCNE classification, 80 (71.4) interventions were proposed to the prescriber. Thirty-nine (48.8%) interventions were accepted, and the acceptance status of 33 (41.3%) interventions was unknown. Only 8 (10.0%) interventions were rejected.

DISCUSSION

This is one of the first retrospective cross-sectional studies to describe the prevalence of drug-related problems in patients admitted to a COVID-19 service in Türkiye. More than half of the hospitalized patients had at least one DRP during the first wave of the COVID-19 pandemic. Patients having DRP had a higher number of drugs. The most common DRPs were related to drug and/or dose selection. Less than half of the clinical pharmacy residents' recommendations were accepted by the physicians.

In our study involving COVID-19 patients, the incidence of DRP was found to be similar to another study performed on COVID-19 patients (1.4 DRP/patient).[18] Similar rates of DRP have been detected in studies involving COVID-19 patients.[5,19,20] DRP rates were found to be higher in studies conducted before the COVID-19 pandemic.[21] The reason for our low DRP rates may be that the study was planned retrospectively during a period under pandemic conditions. Problems with drug safety were identified, including most DRPs, potential drug interactions, ADRs, and high doses. Similar to other studies, the most frequently detected DRP was "treatment safety" (53%) and then "treatment effectiveness" (20%).[19,20] Drug interactions accounted for approximately 40% of the total causes of DRP; the reason for this high rate compared with other studies may be the frequent use of hydroxychloroquine and azithromycin, which are drugs used in the COVID-19 pandemic. The risk of QT prolongation is increased with the combined use of hydroxychloroquine and azithromycin; most clinical pharmacists' recommendations have been this interaction. Proton pump inhibitors (PPIs) are often overprescribed, and overprescribing has continued in the COVID-19 pandemic. Clinical pharmacists advise physicians to optimize PPI use. Long-term use of PPIs has been associated with adverse events such as pneumonia. Analysis of clinical pharmacist interventions in COVID-19 units found that PPI was overprescribe in a similar study.[5] In our study, similar rates of "no drug indication" and "no drug treatment despite the current indication" were found among DRP causes, and it is thought that this may be due to the difficulty of medication reconciliation in pandemic conditions.

In previous studies, DRPs were associated with the presence of comorbidity and polypharmacy.[19-22] The absence of relationships with other variables may be due to the small sample number of patients and DRPs detected.

Half of the interventions proposed because of DRPs were accepted in our study. In different studies conducted before the pandemic, the acceptance rate of the interventions was found to be higher.[21,22] During the COVID-19 pandemic, clinical pharmacists continued to provide services such as medication

Table 2. Patients' biochemical parameters related to COVID-19 (n= 202)

Biochemical parameters	Total patients (n= 202) median (IQR)	Patients with DRP (n= 132) median (IQR)	Patients without DRP (n= 70) median (IQR)	p
ALT	18.0 (11.0-35.0)	17.0 (10.0-36.0)	26.0 (12.5-35.0)	NS
AST	31.0 (21.0-42.0)	20.0 (30.0-42.0)	35.0 (24.0-45.5)	NS
LDH	272.0 (205.0-368.2)	258.0 (201.0-349.0)	311.0 (217.0-427.0)	NS
Ferritin	177.0 (67.4-427.4)	215.0 (67.0-423.2)	138.4 (68.4-467.6)	NS
Procalcitonin	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.2)	NS
CRP	46.5 (12.9-84.2)	40.1 (12.7-95.6)	48.4 (13.3-81.0)	NS
D-dimer	0.9 (0.5-1.6)	0.9 (0.5-1.9)	0.9 (0.5-1.4)	NS
PT	14.0 (13.0-15.6)	14.0 (12.9-15.6)	14.2 (13.4-15.9)	NS
aPTT	29.6 (27.2-31.8)	2.0 (2.0-3.0)	29.6 (26.4-32.1)	NS
Creatinine	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.8 (0.7-1.0)	NS

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, IQR: Interquartile range, DRP: Medication-related problem, NS: No significant

Table 3. DRP based on PCNE V9.00 (n= 132)

	Detailed classification (Code V9.0)	n (%)
The type of DRP (Code V9.0) (n= 264)		
Treatment effectiveness (P1)	Untreated symptoms or indications (P1.3)	46 (17.4)
	Effect of drug treatment not optimal (P1.2)	9 (3.4)
Treatment safety (P2)	Adverse drug event (possibly) occurring (P2.1)	140 (53.0)
Others (P3)	Unnecessary drug treatment (P3.2)	60 (22.7)
	Unclear problem/complaint. Further clarification is necessary (P3.3)	7 (2.6)
	Problem with the cost-effectiveness of the treatment (P3.1)	2 (0.8)
Causes (Code V9.0) (n=270)*		
Drug selection (C1)	Inappropriate combination of drugs or drugs and herbal medication (C1.4)	108 (40.0)
	No indication for the drug (C1.3)	54 (20.0)
	No drug treatment despite existing indication (C1.6)	47 (17.4)
	Inappropriate drug (within guidelines but otherwise contra-indicated) (C1.2)	11 (4.1)
	Inappropriate drug according to the guidelines/formulary (C1.1)	4 (1.5)
	Too many drugs prescribed for indication (C1.7)	4 (1.5)
	Inappropriate duplication of the therapeutic group or active ingredient (C1.5)	3 (1.1)
Drug form (C2)	Inappropriate drug form (for this patient) (C2.1)	3 (1.1)
Dose selection (C3)	Drug dose too high (C3.2)	12 (4.4)
	Drug dose too low (C3.1)	6 (2.2)
	Dosage regimen, too frequent (C3.4)	5 (1.8)
	Dosage regimen, not frequent enough (C3.3)	1 (0.4)
	Dose timing instructions incorrect, unclear, or missing (C3.5)	1 (0.4)
Drug use process (C6)	Inappropriate timing of administration and/or dosing intervals (C6.1)	5 (1.8)
Related patient transport (C8)	Insufficient clinical information about the patient (C8.4)	1 (0.4)
Other (C9)	No obvious cause (C9.3)	3 (1.1)
	No or inappropriate outcome monitoring (including therapeutic drug monitoring) (C9.1)	2 (0.8)
Proposed interventions (Code V9.0) (n= 112)		
At the prescriber level (I1)	Intervention proposed to the prescriber (I1.3)	54 (19.9)
	Prescriber informed only (I1.1)	48 (17.7)
At the drug level (I3)	Drug stopped I3.5	5 (1.8)
	Dosage changed to... (I3.2)	2 (0.7)
	Drug changed to... (I3.1)	1 (0.4)
	Formulation changed to... (I3.3)	1 (0.4)
	Instructions for use changed to... (I3.4)	1 (0.4)
Acceptance of the intervention proposals (Code V9.0) (n= 80)		
Intervention accepted (by prescriber or patient) (A1)	Intervention accepted and fully implemented (A1.1)	22 (27.5)
	Intervention accepted; implementation unknown (A1.4)	12 (15.0)
	Intervention not accepted: no agreement (A2.2)	7 (8.8)
	Intervention accepted, partially implemented (A1.2)	4 (5.0)
	Intervention accepted but not implemented (A1.3)	1 (1.3)
	Intervention not accepted: other reason (specify) (A2.3)	1 (1.3)
Other (no information on acceptance) (A3)	Intervention proposed, acceptance unknown (A3.1)	33 (41.3)

*More than one cause was determined for each DRP, DRP: Medication-related problem, PCNE: Pharmaceutical Care Network Europe

reconciliation, medication review, therapeutic drug monitoring, patient education, and counseling for patients hospitalized with COVID-19 over the phone or by working remotely.[7,23] The limited performance of clinical pharmacy services due to situations such as the inability to take a medication history from the patient, the patients being in isolation conditions, the clinical pharmacist's inability to visit the patient and remote work, and the daily change of the physicians who follow the patients and the pharmacists who make suggestions may have caused the acceptance rates to be low. Because of the first wave of the pandemic, the strict implementation of protective measures, and the remote working conditions, acceptance rates could not be followed very well in resolving drug-related problems. In addition, a published articlestated that the acceptance rate of the recommendations made by pharmacists during the pandemic was lower than before the pandemic due to less effective communication and the need for more intensive follow-up to be accepted.[7]

Due to the interventions being proposed verbally, the proposal and following the acceptance status made during the transfers between the physicians and pharmacists may have been skipped. In this regard, the WHO recommends that patients' status, medication, and treatment plans be communicated in detail using a standard communication technique during care transitions to ensure a standardized handover.[5]

Clinical pharmacists can quickly develop telehealth strategies by analyzing the current situation with their professional expertise in pandemics. In this context, it can provide innovative pharmacy services such as telehealth counseling, guideline development, health education *via* multi-media, and evidence-based drug evaluation.[23]

In subsequent studies, clinical pharmacists may continue to participate in services such as medication reconciliation, medication review, discharge education, and medication counseling, as they did in periods other than the pandemic, but this time taking more precautions. If the necessary infrastructure is provided, the aforementioned services can also be delivered to patients by phone or video calls.

This study had limitations due to the retrospective and observational definition of DRPs. The study was conducted in a single center with a small number of patients; therefore, the results obtained here may not be generalizable. In the follow-up of the patients, inaccurate information was removed, and the information that was sure to be correct was evaluated. We could not determine for each patient whether an adverse drug case identified in the patient record and clinical pharmacist note is actually related to that medication or not. Therefore, adverse drug events may be underreported. However, our study is important because it shows that DRPs continue in pandemic conditions and there is a need for clinical pharmacy services.

CONCLUSION

While this study draws attention to the importance of DRPs in the treatment of COVID-19, it also revealed that clinical pharmacists should work as a part of the healthcare team in very difficult conditions such as pandemics. Further studies will be helpful to determine DRP levels in COVID-19 patients.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Clinical Research Ethical Committee of the Marmara University Faculty of Medicine (approval number: 09.2020.668, date: 12.06.2020). The required permission to conduct this study was obtained from the Ministry of Health, The Republic of Türkiye.

Informed Consent: Since the study was retrospective, informed consent was not obtained from patients and/or caregivers.

Authorship Contributions

Concept: D.Ü., C.E., M.Y.D., Y.E.A., B.Ö., M.S., Design: D.Ü., C.E., M.Y.D., Y.E.A., B.Ö., S.K., V.K., M.S., Data Collection or Processing: D.Ü., C.E., M.Y.D., Y.E.A., B.Ö., E.E.İ., B.E.Ş., D.K., U.S., E.T.T., Analysis or Interpretation: D.Ü., C.E., M.Y.D., B.Ö., V.K., M.S., Literature Search: D.Ü., C.E., M.Y.D., Y.E.A., B.Ö., E.E.İ., Writing: D.Ü., C.E., M.Y.D., Y.E.A., B.Ö., E.E.İ., B.Ö., B.E.Ş., D.K., U.S., E.T.T., S.K., V.K., M.S.

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