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ORIGINAL ARTICLE

Evaluation of Drug-Related Problems of Intensive Care Unit Patients by Clinical Pharmacists: A Retrospective Study

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ABSTRACT

Objectives: The study aimed to identify drug-related problems (DRPs) and risk factors associated with the emergence of DRPs in intensive care unit (ICU) patients.

Materials and Methods: This retrospective study included patients in the anesthesiology and reanimation ICU of a university-affiliated tertiary care hospital. DRPs identified by clinical pharmacists were classified using the Pharmaceutical Care Network Europe Classification for DRPs version 9.1. The association between various patient-related factors, and having DRPs were evaluated.

Results: In total, 222 patients were included in the study, 128 of which were male (57.7%). The number of DRPs was 388 in 135 patients (1.75 ± 2.47 DRPs per patient). The group in which at least 1 DRP was identified, the duration of hospitalization was longer than in the group in which no DRP was identified ($p < 0.001$). In the groups in which there was the presence of mechanical ventilation support at admission or mortality, the mean DRP count was significantly higher than that in the other group ($p < 0.05$). Age, duration of hospitalization, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission had positive relationships with the DRP count, but the Glasgow Coma Scale (GCS) showed a negative relationship ($p < 0.05$). According to the binary logistic regression analysis ($p < 0.001$), in which the age of the patient, GCS score, APACHE II score at admission, duration of hospitalization, and presence of mechanical ventilation support at admission were included, only the APACHE II score at admission and duration of hospitalization significantly affected the emergence of DRPs. The major problem was related to treatment effectiveness (47.9%), followed by treatment safety problems (29.9%). The major causes of these problems were dose selection (44.0%) and drug selection (36.8). Interventions were made at the drug (97.2%) and prescriber level (2.3%). The acceptance rate of interventions and resolution rate of the DRPs were 93.6% and 85.1%, respectively. The top three medications that caused DRPs the most were as follows: meropenem, colistin, and piperacillin/tazobactam.

Conclusion: Clinical pharmacists can detect and treat DRPs quickly. Our analysis shows that clinical pharmacy services are needed in high-DRP wards like ICU.

Keywords: Clinical pharmacist, critical illness, intensive care units, medication errors

INTRODUCTION

According to the Pharmaceutical Care Network Europe Association (PCNE), a drug-related problem (DRP) is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes".[1] Drug-drug interactions, adverse drug events (ADEs), and medication errors can be classified as DRPs.[2] DRPs and ADEs are frequently encountered in intensive care units (ICUs).[3] Treatments administered to critically ill patients may put them at risk in terms of these types of medical errors.[4] A previously conducted study claims that almost half of the hospitalizations are related to DRPs and ADEs.[5] A systematic review conducted in 2007 shows that 46.5% of the ADEs are preventable, and 16.0% of these are emerging from medication errors.[6] There

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are studies that include the interventions of pharmacists in order to identify and solve the DRPs seen in ICUs.[7-9] In a study, the interventions of clinical pharmacists decreased DRP rates in geriatric patients.[9] Clinical pharmacists can help determine and solve DRPs early.[10] The integration of clinical pharmacists into the existing healthcare system, it will be possible to better detect and tackle DRPs.

The study aimed to identify DRPs and risk factors associated with the emergence of DRPs in ICU patients.

MATERIALS AND METHODS

Study design and setting

The current retrospective study was conducted in the reanimation ICU with a 26-bed capacity of a university-affiliated tertiary care hospital in Malatya, Türkiye between May 2022 and December 2022. In the ICU, the physicians in charge consist of two professors, an assistant professor, and four physicians. Specialists and resident physicians also work alternate shifts. The working hours are between 8 a.m. and 5 p.m. in the ICU. Two clinical pharmacy residents participated in weekday rounds with ICU and infectious diseases physicians, nurses, and technicians. The recommendations for DRPs made by the clinical pharmacy residents were recorded. The classification of DRPs according to the PCNE classification system was performed by reaching a consensus among clinical pharmacy residents.

Ethics approval

This study was conducted in line with the principles of the Declaration of Helsinki. Approval was granted by the İnönü University Scientific Research and Publication Ethics Committee (approval number: 4521, date: 11.04.2023). Participant consent was obtained from all patients included in the study.

Participants

All patients hospitalized for at least 24 hours in the ICU were included in the study. Patients whose hospitalization and discharge occurred on the same weekend or when the clinical pharmacy residents were absent from the ICU, or patients whose data were missing, were excluded from the study.

Data collection

The hospital's electronic database was used to obtain information about the patients' demographics, diagnoses, laboratory results, Glasgow Coma Scale (GCS) scores, Acute Physiology and Chronic Health Evaluation (APACHE) II scores at admission, duration of hospitalization, the status of mechanical ventilation support at admission, and types of admission. Daily medication charts were obtained from patient files. Admission diagnoses and drugs associated with DRPs were classified using the International Classification of Diseases, 10th revision (ICD-10) and the Anatomical Therapeutic Chemical (ATC) Classification System, respectively. The UpToDate®, Micromedex®, Lexicomp®, Sanford Antimicrobial Guide®, CredibleMeds®, and LiverTox® databases were used to identify DRPs. The identified DRPs were classified using the PCNE Classification for DRPs, version 9.1.

Outcomes

The primary outcomes of this study were determining the DRPs, the acceptance rates of the interventions, and the resolution rates of the DRPs administered by clinical pharmacists in the ICU. The secondary outcomes of this study are determining the most frequent DRPs and the association between DRPs and various patient-related factors. DRPs were classified using the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), revised in October 2022 Index revised in October 2022 to determine the extent to which patients were harmed.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) v27.0. The normality of the continuous data was tested using the Kolmogorov-Smirnov test, and it was observed that none of the data was distributed normally; thus, non-parametric tests were applied. Continuous and categorical data were presented as median (25th percentile-75th percentile) and number (percentage), respectively. All the data in this study were present. The continuous data between the two groups were compared using the Mann-Whitney U test, whereas the categorical data were compared using Fisher's exact test. The presence of a correlation between the two continuous variables was explored using Spearman's correlation test. The correlation coefficient value was interpreted as follows: Correlation coefficient < 0.3 was interpreted as poor; correlation coefficient 0.3 to 0.5 was interpreted as fair; correlation coefficient 0.6 up to 0.8 was interpreted as moderately strong; and correlation coefficient ≥ 0.8 was interpreted as very strong linear relationship.[11] Binary logistic regression analysis was performed to examine the extent to which various patient-related factors affect the emergence of DRP. A p value of 0.05 was considered statistically significant.

RESULTS

During the study period, 418 patients were admitted to the ICU. Of the 196 patients, 196 were excluded from the study because of admission/discharge on the same weekend or because the clinical pharmacy residents were absent from the ICU, or whose data were missing. Finally, the study included 222 patients, of whom 57.7% were men. One or more DRPs were identified in 135 patients, for a total of 388 DRPs (1.75 ± 2.47 DRPs per patient). The total number of patient days was 4,868 (79.7 DRPs per 1000 patient days). The characteristics of the patients are summarized in Table 1.

The top 4 admission diagnoses classified according to the ICD-10 are given in Table 2.

The number of DRPs were compared according to the presence of mechanical ventilation support, mortality, and surgery and are presented in Table 3.

The correlations between DRP count, duration of hospitalization, age, GCS score at admission, and APACHE II score at admission are given in Table 4.

Table 1. Characteristics of the patients

Characteristic	Total	DRPs identified	No DRPs were identified	*p* value
Patients (n, %)	222 (100.0)	135 (60.8)	87 (39.2)	
Sex (n, %)				
Male Female	128 (57.7) 94 (42.3)	80 (59.3) 55 (40.7)	48 (55.2) 39 (44.8)	0.580[a]
Age, years (median, (25th percentile-75th percentile)]	66.50 (50.00-79.00)	69.00 (55.00-78.00)	61.00 (41.00-79.00)	0.053[b]
Duration of hospitalization, days [median, (25th percentile-75th percentile)]	10.00 (5.00-26.25)	15.00 (7.00-36.00)	6.00 (4.00-13.00)	<0.001[b]
Presence of surgery (n, %)	94 (42.3)	58 (43.0)	36 (41.4)	0.890[a]
Presence of mechanical ventilation support at admission (n, %)	89 (40.1)	64 (47.4)	25 (28.7)	0.008[a]
Mortality (n, %)	85 (38.3)	64 (47.4)	21 (24.1)	<0.001[a]
Total GCS at admission [median, (25th percentile-75th percentile)]	11.00 (3.00-15.00)	9.00 (3.00-14.00)	14.00 (3.00-15.00)	<0.001[b]
Total APACHE II Score upon admission [median, (25th percentile-75th percentile)]	15.00 (8.00-24.00)	18.00 (10.00-26.00)	10.00 (5.00-18.00)	<0.001[b]
Admitted from (n, %)				
Emergency Another ward/hospital	90 (40.5) 132 (59.5)	44 (32.6) 91 (67.4)	46 (52.9) 41 (47.1)	0.003[a]
CRP level upon admission (upper limit of normal* is 0.351 mg/dL) (n, %)				
Normal High	41 (18.5) 181 (81.5)	22 (16.3) 113 (83.7)	19 (21.8) 68 (78.2)	0.376[a]
PCT at admission (upper limit of normal* is 0.5 ng/mL) (n, %)				
Normal High	98 (44.1) 124 (55.9)	53 (39.3) 82 (60.7)	45 (51.7) 42 (48.3)	0.073[a]
SCr level upon admission (upper limit of normal* is 1.25 mg/dL) (n, %)				
Normal High	118 (53.2) 104 (46.9)	66 (48.9) 69 (51.1)	52 (59.8) 35 (40.2)	0.130[a]

[a]Fisher's exact test, [b]Mann-Whitney U test, *The upper limit of normal values was obtained from the hospital's laboratory results.
APACHE II: Acute Physiology and Chronic Health Evaluation II, CRP: C-reactive protein, GCS: Glasgow Coma Scale, PCT: Procalcitonin, SCr: Serum creatinine, DRP: Drug-related problem

Table 2. The top 4 diagnoses classified according to the ICD-10

Diagnosis	n (%)
Subarachnoid hemorrhage	15 (6.8)
Sepsis	13 (5.9)
Bacterial pneumonia	12 (5.4)
Car occupant (any) injured in unspecified traffic accident	12 (5.4)

ICD: International Classification of Diseases

Table 3. Comparison of mean DRP counts according to various patient-related factors

Factor	Total (mean ± SD)	Yes (mean ± SD)	No (mean ± SD)	*p* value
Presence of mechanical ventilation support	1.75 ± 2.47	2.20 ± 2.50	1.44 ± 2.42	< 0.001[a]
Mortality		2.52 ± 2.81	1.27 ± 2.12	< 0.001[a]
Presence of surgery		2.11 ± 2.97	1.48 ± 2.01	0.254[a]

[a]Mann-Whitney U test, DRP: Drug-related problem, SD: Standard deviation

On the basis of binary logistic regression analysis, the effects of age, GCS score at admission, APACHE II score at admission, duration of hospitalization, and presence of mechanical ventilation support at admission on the likelihood of DRP were determined. The logistic regression model was significant, $\chi^2(5) = 42.132$, $p < 0.001$. The Hosmer-Lemeshow test showed that the data fit the model well, $\chi^2(8) = 12.579$, $p = 0.127$. The model accurately identified 73.9% of the cases and explained 23.4% (Nagelkerke R^2) of the variance in DRP emergence. An increase of 1 unit in the APACHE II score at admission and the duration of hospitalization increased the likelihood of the emergence of DRP by 1.042 (95% CI 1.000-1.086) and 1.032 (95% CI 1.012-1.051), respectively. However; age, GCS score at admission, and the presence of mechanical ventilation support at admission did not have a statistically significant effect on the risk of the emergence of DRP.

The DRPs were classified according to the NCC MERP Index in an attempt to visualize the harm status, and the results are given in Table 5.

The DRPs were classified according to PCNE v9.1, of which 205 (52.8%) were potential DRPs and 183 (47.2%) were actual DRPs. Among the actual DRPs, 168 (91.80%) of them were accepted and 153 (83.61%) of them were solved. The related results are presented in Table 6.

According to the ATC classification system, the three classes most closely related to DRPs were as follows: antibacterials for systemic use (n= 104; 26.8%), general nutrients (n= 45; 11.6%), and IV solution additives (n= 25; 6.4%). Meropenem (24, 23.1%), colistin (20, 19.2%), and piperacillin/tazobactam (13, 12.5%) were the top three antibacterial medications most closely associated with DRPs. In total, 116 DRPs associated with possible ADEs were identified. The first three drugs for which interventions were made to assess possible ADEs were meropenem (14, 12.1%), colistin (13, 11.2%), and piperacillin-tazobactam (9, 7.8%). The examples of clinical pharmacist interventions are presented in Table 7.

Table 4. Correlations between various patient characteristics and DRP count

Patient characteristics	Spearman's rho	Orientation and degree of association	*p* value
Duration of hospitalization	0.446	Positive-oriented fair	< 0.001
Age	0.133	Positive-oriented poor	0.048
GCS upon admission	-0.302	Negatively oriented fair	< 0.001
APACHE II score upon admission	0.308	Positive-oriented fair	< 0.001

APACHE II: Acute physiology and chronic health evaluation, GCS: Glasgow Coma Scale, DRP: Drug-related problem

Table 5. Distribution of DRPs according to NCC MERP index

Category	Explanation	n (%)	Harm status, n (%)
A	Circumstances or events that have the capacity to cause errors	205 (52.8)	No error, 205 (52.8)
B	An error occurred, but it did not reach the patient	2 (0.5)	Error, no harm, 142 (36.6)
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or intervention to preclude harm	140 (36.1)	
E	An error that may have contributed to or resulted in temporary harm to the patient	20 (5.2)	Error, harm, 41 (10.6)
F	An error that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization	21 (5.4)	

DRP: Drug-related problem, NCC MERP: National Coordinating Council for Medication Error Reporting and Prevention

Table 6. Classification of DRPs according to PCNE classification system v9.1

Domains	Code	Subdomains	n (%)
Problems			388 (100.0)
	Treatment effectiveness		186 (47.9)
	P1.3	Untreated symptoms or indications	95 (24.5)
	P1.2	Effect of drug treatment not optimal	90 (23.2)
	P1.1	No effect of drug therapy despite correct use	1 (0.3)

Table 6. Continued

Domains	Code	Subdomains	n (%)
	Treatment safety		116 (29.9)
	P2.1	Adverse drug event (possibly) is occurring	116 (29.9)
	Other		86 (22.2)
	P3.1	Unnecessary drug-treatment	65 (16.8)
	P3.2	Unclear problem/complaint	21 (5.4)
Causes			418 (100.0)
	Dose selection		184 (44.0)
	C3.2	Drug dose of a single active ingredient	59 (14.1)
	C3.1	Drug dose too low	55 (13.2)
	C3.4	Too frequent dosage regimen	46 (11.0)
	C3.3	Dosage regimen not frequent enough	22 (5.3)
	C3.5	Dose timing instructions are incorrect, unclear, or missing	2 (0.5)
	Drug selection		154 (36.8)
	C1.5	No or incomplete drug treatment in spite of existing indication	96 (23.0)
	C1.2	No indication for the drug	26 (6.2)
	C1.3	Inappropriate combination of drugs, herbal medications, and dietary supplements	15 (3.6)
	C1.4	Inappropriate duplication of therapeutic groups or active ingredients	11 (2.6)
	C1.1	Inappropriate drug according to the guidelines/formularies	3 (0.7)
	C1.6	Too many different drugs and active ingredients prescribed for indication	3 (0.7)
	Other		38 (9.1)
	C9.2	Other cause	17 (4.1)
	C9.3	No obvious cause	16 (3.8)
	C9.1	No or inappropriate outcome monitoring	5 (1.2)
	Treatment duration		34 (8.1)
	C4.2	Too long treatment duration	34 (8.1)
	Patient transfer-related		4 (1.0)
	C8.1	Medication reconciliation	4 (1.0)
	Drug form		2 (0.5)
	C2.1	Inappropriate drug form/formulation (for this patient)	2 (0.5)
	The drug use process		2 (0.5)
	C6.1	Inappropriate timing of administration or dosing intervals by a health professional	1 (0.2)
	C6.6	Drug administration *via* the wrong route by a health professional	1 (0.2)
Planned interventions			388 (100.0)
	At the drug level		377 (97.2)
	I3.2	Dosage changed to	171 (44.1)
	I3.6	Drug started	101 (26.0)
	I3.5	Paused or stopped drug	77 (19.9)
	I3.1	Drug changed to	19 (4.9)
	I3.4	Instructions for use changed to	7 (1.8)
	I3.3	The formula was changed to	2 (0.5)

Table 6. Continued

Domains	Code	Subdomains	n (%)
	The prescriber level		11 (2.8)
	I1.3	Intervention proposed to the prescriber	9 (2.3)
	I1.1	The prescriber is informed only	2 (0.5)
Intervention acceptance			388 (100.0)
	Intervention accepted		363 (93.6)
	A1.1	Intervention accepted and fully implemented	346 (89.2)
	A1.2	Intervention accepted, partially implemented	11 (2.8)
	A1.3	Intervention accepted but not implemented	4 (1.0)
	A1.4	Intervention accepted, implementation unknown	2 (0.5)
	Intervention not accepted		24 (6.2)
	A2.2	Intervention not accepted, no agreement	20 (5.2)
	A2.1	Intervention not accepted, not feasible	4 (1.0)
	Other		1 (0.3)
	A3.2	Intervention not proposed	1 (0.3)
DRP status			388 (100.0)
	Solved		330 (85.1)
	O1.1	Problem totally solved	330 (85.1)
	Not solved		32 (8.3)
	O3.2	Problem not solved, lack of physician cooperation	21 (5.4)
	O3.4	No need or possibility to solve the problem	7 (1.8)
	O3.3	Problem not solved, intervention not effective	4 (1.0)
	Not known		22 (5.7)
	O0.1	Problem status is unknown	22 (5.7)
	Partially solved		4 (1.0)
	O2.1	Problem partially solved	4 (1.0)

DRP: Drug-related problem, PCNE: Pharmaceutical Care Network Europe Association

Table 7. The sample pharmacist interventions at the drug and DRP levels

Cause	Drug	Pharmacist intervention
Dose selection		
C3.2 High drug dose of a single active ingredient	Piperacillin-tazobactam	The patient was administered 4.5 g q6h piperacillin-tazobactam in spite of hemodialysis therapy. The pharmacist recommended changing the drug dosage to 2.25 g every 6 hours
C3.1 Too low a drug dose	Valproic acid	The patient was administered 500 mg of valproic acid q12h and the serum valproic acid level was 29 mg/L. The pharmacist recommended changing the drug dosage to 500 mg every 8 hours
C3.4. Dosage regimen too frequent	Pantoprazole	The patient was administered intravenous pantoprazole 40 mg every 12 hours despite the absence of gastrointestinal bleeding signs. The pharmacist recommended changing the drug dosage to 40 mg every 24 hours
C3.3 Dosage regimen not frequent enough	Meropenem	The patient was administered 1 g of meropenem every 12 hours despite the absence of renal impairment. The pharmacist recommended changing the drug dosage to 1 g every 8 hours
C3.5 Dose timing instructions that are incorrect, unclear, or missing	Meropenem	The patient was administered 30 min of meropenem infusion therapy despite the presence of microorganism resistance. The pharmacist recommended increasing the infusion duration to 3 hours

Table 7. Continued

Cause	Drug	Pharmacist intervention
Drug selection		
C1.5 No or incomplete drug treatment despite an existing indication	Levetiracetam	The patient admitted with subdural hemorrhage did not receive prophylactic antiseizure medication. The pharmacist recommended 1 g of levetiracetam every 12 hours for a duration of 7 days
C1.2. No indication for drugs	Cefazoline	The patient admitted for postoperative thyroidectomy was administered antibacterial prophylaxis. The pharmacist recommended discontinuing cefazolin therapy because clean procedures do not require antibacterial prophylaxis
C1.3 Inappropriate combination of drugs, herbal medications, and dietary supplements	Clarithromycin	Clarithromycin and phenytoin therapy were concomitantly administered. The pharmacist recommended replacing clarithromycin with azithromycin, which does not interact with phenytoin
C1.4 Inappropriate duplication of therapeutic groups or active ingredients	Furosemide	The patient with decompensated heart failure was administered intravenous and oral furosemide therapy concomitantly. The pharmacist recommended discontinuing oral furosemide
C1.1 Inappropriate drug according to the guidelines/formularies	Dexamethasone	A patient admitted with a brain tumor was administered dexamethasone therapy in an attempt to reduce the cerebral edema. The pharmacist recommended stopping dexamethasone therapy because it was of no use in this case
C1.6 Too many different drugs and active ingredients prescribed for indication	Tramadol	The patient was administered fentanyl and tramadol concomitantly as part of analgosedation therapy. The pharmacist recommended stopping tramadol therapy
Other		
C9.2 Other causes	Normal saline	The patient was administered normal saline despite the serum sodium level of 161 mmol/L. The pharmacist recommended replacing normal saline with 1/2 normal saline therapy
C9.3 No obvious cause	Rivaroxaban	The patient was administered rivaroxaban. The pharmacist recommended that the drug be withheld for 24 hours before surgery
C9.1 No or inappropriate outcome monitoring	Valproic acid	The patient was administered valproic acid and meropenem therapy concomitantly; however, the valproic acid level was not monitored. The pharmacist recommended therapeutic drug monitoring of valproic acid
Treatment duration		
C4.2 Too long treatment duration	Hydrocortisone	The patient was administered 50 mg q6h hydrocortisone therapy because of septic shock; however, the duration of therapy was > 7 days. The pharmacist recommended discontinuation of hydrocortisone therapy with a taper
Patient transfer-related		
C8.1 Medication reconciliation problem	Valsartan-hydrochlorothiazide	For hypertensive patients, the pharmacist recommended the administration of home antihypertensive medication
Drug form		
C2.1 Inappropriate drug form/formulation (for this patient)	Levodopa-benserazide	Being fed via a nasogastric tube, the patient is prescribed levodopa-benserazide capsules. The pharmacist recommended replacing the capsule form with the tablet form because capsules should not be opened while tablets are crushed
The drug use process		
C6.1 Inappropriate timing of administration or dosing interval by a health professional	Pyridostigmine	The patient with diarrhea was administered pyridostigmine and continuous feeding. The pharmacist recommended replacing continuous feeding with bolus feeding and administering pyridostigmine in combination with bolus feeding
C6.6 Drug administration via the wrong route by a health professional	Tamsulosin	For patients who could not take the tamsulosin capsule orally, it was administered by opening the capsule. The pharmacist recommended replacing tamsulosin with doxazosin, which can be crushed and administered via a nasogastric tube

DISCUSSION

To the best of our knowledge, this is the first DRP study to have been performed in the anesthesiology and reanimation ICU of a tertiary care hospital in Türkiye that included clinical pharmacist interventions for DRP resolution.

Since clinical pharmacy specialization is a new healthcare profession in Türkiye, this study is important to enlighten pharmacists who are considering specializing in critical care pharmacy in the future.

This study has a number of strengths, one of which is that the PCNE classification was determined by reaching a consensus between two clinical pharmacists, which helped reduce the possibility of bias. Another strength of this study is that it classifies DRPs that occur in ICUs, provides recommendations for the management of DRPs, and classifies the severity of medication errors using the NCC MERP. Besides, this study provides a sample pharmacist intervention table classified according to the causes of specific DRPs, which may be especially useful for those who would like to increase their expertise in the critical care pharmacy field.

Interpretation

In this study, at least one DRP was identified in 60.8% of patients, with an average of 1.75 DRPs per patient. In an ICU study conducted in 2022, at least one DRP was detected in 71.5% of patients, and 1.36 DRPs were found in each patient.[12] In another study, 69.8% of patients had at least one DRP, and the average DRP count per patient was 1.36.[13] However, in another study conducted in the cardiology service in 2022, at least 1 DRP was detected in 54.3% of patients, and the DRP count per patient was found to be 1.84.[14] This difference may be due to the fact that the rate of patients with at least 1 DRP was higher due to the inability of critically ill patients in the ICU to continue their medications at home. At the same time, the fact that the intensive care team in which the study was conducted was not familiar with the clinical pharmacist recommendations was one of the factors affecting the detected DRP numbers.[15]

In our study, the mean DRP counts were significantly higher in the group receiving mechanical ventilation support than in the group not receiving mechanical ventilation support (p = 0.008). In a study conducted in Türkiye in 2022, it was found that receiving mechanical ventilation support increased the incidence of DRP by 3,435 times ($p < 0.001$).[16] Since mechanical ventilation support requires additional drug therapy (stress ulcer prophylaxis, analgosedation, *etc.*), it is expected to increase the incidence of DRP.

A high APACHE II score and a low GCS score indicate that the patient's condition is critical. Given the complexity of pharmacotherapy in such patients, extra attention is required regarding DRPs. According to our findings, the mean APACHE II score and GCS score were higher in the group in which DRP was identified than in the group in which DRP was not identified.

Due to alterations in drug pharmacokinetics and organ function, critically ill patients are at increased risk of ADEs.[17] At the same time, critically ill patients experience many physiological changes that can affect drug metabolism and excretion. Organ dysfunction, particularly renal failure, may lead to increased ADEs.[18] Given these changes, the incidence of DRP may be higher in critically ill patients than in the general population. In a study examining the causes of DRPs, C1 drug selection (41.3%) and C3 drug selection were the most common causes (29.0%).[19] In another study, DRPs were categorized according to their causes, and C3-dose selection (39.7%) and C5-drug use process (32.7%) were determined to be the most prominent causes.[20] In our study, C3-drug selection (44.0%) and C1-drug selection (36.8%) associated DRPs were the most prevalent. These differences may be due to differences in countries, populations, and healthcare providers.

With the intervention of clinical pharmacists, potential medication errors and adverse drug reactions can be effectively prevented, and patients' drug safety can be further improved.[21] Implementation of interventions with pharmacists participating in a multidisciplinary team can play a crucial role in executing drug protocols and preventing drug-related issues.[22] Among the pharmacist interventions for DRPs in studies conducted on geriatric[23] and neurological[24] patients, I1-at prescriber level interventions had the highest rate. In our study, most interventions were performed at the I3 level (97.1%). We believe that the biggest reason for the difference is that physicians in the service area, especially infectious disease specialists, allow clinical pharmacists to make changes in drug dose adjustments.

It has been observed that the acceptance rate of recommendations in previous studies exceeds 90%.[23,25-27] In another study, the acceptance rate of recommendations for DRPs was 100.0%, and 78.4% of DRPs were completely resolved.[28] The acceptance rate of interventions in our study was 93.6%, and 85.1% of the DRPs were completely resolved, which is in line with the literature.

In a study, antibiotics were found to be the drug group that caused the most DRP, followed by antiplatelet drugs and PPIs.[29] In another study, the most common drug groups causing DRP were antihypertensive drugs, antithrombotic drugs, and statins.[30] In our study, the most common drug groups causing DRP were systemic antibacterials (26.8%), general nutrients (11.6%), and IV solution additives (6.4%).

In a study conducted in 2020, it was determined that due to drug dosing error, sulfamethoxazole/trimethoprim caused the most DRP,[31] and in our study, meropenem (23.1%), colistin (19.2%), and piperacillin/tazobactam (12.5%) were found to be the drugs that caused the most DRP. The main reason why, especially meropenem and colistin, have been identified as drugs that cause a lot of DRP is the high frequency of acinetobacter-induced infections in the ICU and the use of these drugs in the treatment of these infections. In addition, colistin requires frequent renal dose adjustment.

In many studies, each DRP was graded using the NCC MERP, which is an index that categorizes medication errors to determine their severity.[32] In a study conducted with medical ward patients, DRPs defined according to the NCC MERP Index

were classified according to their severity rates, with 45.9% in category B, 41.5% in category C, and 12.7% in category D.[33] In our study, the distribution of DRPs according to the NCC MERP was 52.8% in category A, 36.1% in category D, 5.3% in category E, and 5.4% in category F. Temporary harms were detected early, and necessary interventions were made by clinical pharmacists so that these harms could not be converted to permanent harm. This difference across studies may stem from the nature of the place where healthcare is provided and the diversity of patient profiles.

In a study conducted in the internal medicine ward in Türkiye, a positive fair (r = 0.411) correlation was found between DRP counts and age, and a positive-oriented fair (r = 0.302) relationship was found between DRP counts and the length of stay in the hospital.[34] In this study, the DRP counts had a positive poor (r = 0.133) correlation with age and a positive fair (r = 0.446) correlation with the duration of hospitalization. Changes in pharmacokinetics and pharmacodynamics associated with aging can be noticed in geriatric patients, which explains the higher incidence of DRPs in this patient population. On the other hand, the patient's risk of acquiring DRP may increase if they are hospitalized for a longer duration.

In a study conducted in 2018 in which 474 older patients were included, the multivariate analysis showed that the length of stay increased the presence of DRP by 1,086 times ($p < 0.05$).[23] However, in a study published in 2019 in which 162 ICU patients were included, according to the multinomial logistic regression analysis, the length of stay had no significant effect on the presence of DRP ($p > 0.05$).[13] However, in our study, the duration of hospitalization increased the presence of DRP by 1.042 times ($p < 0.05$). This difference across the aforementioned studies may have arisen from the diversity of sample sizes. Martins et al.[13] may have made a type 2 error in detecting the effect of length of stay on the presence of DRP due to their relatively small sample size.

Further research

Further studies should be conducted to obtain more generalizable results in which a larger number of patients are included and more than one center is included. More advanced research on the risk factors associated with the emergence of DRPs should be conducted to inform healthcare providers. In addition, more studies are needed to demonstrate the impact of clinical pharmacy services in different areas of the health system, particularly in ICUs.

Study limitations

One of the limitations of the study was that it was conducted in a single center with a relatively small number of patients; so, the generalizability of the study results is limited. The identified DRP counts may be lower than the actual counts because clinical pharmacists were absent from the ward on weekends and holidays.

CONCLUSION

DRPs are adverse conditions that can cause significant changes in the treatment courses of patients. Clinical pharmacists play a key role in the timely detection and resolution of DRPs. Clinical pharmacists can offer the most appropriate solutions by providing suggestions for DRPs in line with the current literature. Our study showed that clinical pharmacy services are necessary in wards, such as ICUs, where the rate of DRPs may be high.

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Ethics

Ethics Committee Approval: This study was conducted in line with the principles of the Declaration of Helsinki. Approval was granted by the İnönü University Scientific Research and Publication Ethics Committee (approval number: 4521, date: 11.04.2023).

Informed Consent: Participant consent was obtained from all patients included in the study.

Authorship Contributions

Surgical and Medical Practices: M.B., Concept: Z.Ü.G., M.B., Design: Z.Ü.G., M.B., Data Collection or Processing: A.Ç., H.M., Analysis or Interpretation: A.Ç., H.M., Literature Search: A.Ç., H.M., Writing: A.Ç., H.M., Z.Ü.G.,

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