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Original Article

The evaluation and classification of drug-related problems by a clinical pharmacist in an internal diseases intensive care unit: A prospective cohort 7-month study*

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ABSTRACT

Background and Aims: Drug-related problems can cause morbidity and mortality as well as increase health-care costs. Clinical pharmacists provide many benefits to healthcare systems by detecting, decreasing, and preventing drug-related problems. It was aimed to determine and classify drug-related problems and determine risk factors for drug-related problems.

Methods: Drug-related problems were evaluated prospectively between August 16, 2021, and March 16, 2022, in 257 patients during their hospital stay who were hospitalized in the internal diseases intensive care unit and took at least one drug. Patients who were not administered any drug or who were younger than 18 were excluded from the study. The Pharmacetical Care Network Europe v.9 method was utilized to classify these problems. Clinical and demographic characteristics of patients with and without drug-related problems were compared by statistical analysis. Risk factors of drug-related problems were determined by logistic regression analysis.

Results: At least one drug-related problem was detected in 157 of the 257 patients and a total of 399 drug-related problems were recorded. 399 recommendations were made, and 349 (87.5%) of these were accepted and 50 (12.5%) were not accepted. Drug selection (C1) was the most common cause of drug-related problems at 42.2%, and dose selection (C3) followed this by 41.5%. The results of regression analysis showed that atrial fibrillation (OR: 2.985, CI: 1.158-7.692), hematopoietic stem cell transplantation (OR: 3.883, CI: 1.256-11.999), antibacterial drugs (OR: 3.285, CI: 1.563-6.904), or polypharmacy (OR: 3.955, CI:1.207- 11.071) were risk factors of drug-related problems.

Conclusion: The most common drug-related problem category was found as treatment safety and the causes of them were found as drug selection and dose selection. Clinicians should pay attention when prescribing new drugs to patients with atrial fibrillation and a history of hematopoietic stem cell transplantation. Furthermore, clinicians and clinical pharmacists should pay attention if polypharmacy and antibacterial drugs are present in medical therapies.

Keywords: Clinical pharmacy, drug-related problem, intensive care unit

INTRODUCTION

Drugs have many benefits to patient care, but they could also have detrimental effects such as adverse drug reactions, and drug-drug interactions. These drug-related problems (DRPs) can cause morbidity and mortality as well as increase healthcare costs (Ruths, Viktil, & Blix, 2007). Drug-related problem as defined to be an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes by Pharmaceutical Care Network Europe Association (Pharmaceutical Care Network Europe Association, 2023). There were many risk factors for DRPs such as polypharmacy, polymorbidity, anticoagulant usage, renal failure, and hepatic failure (Kaufman, Stämpfli, Hersberger, & Lampert, 2015). Pharmaceutical care by clinical pharmacists is aimed at detecting, decreasing, and preventing DRPs (Viktil & Blix, 2008). Detection and classification of DRPs have many advantages. Raising awareness about the frequency and source of DRPs; increasing the knowledge of using medicine with care among clinicians, pharmacists, and patients by feedback; developing pharmaceutical

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care practice and research by documentation and classification of DRPs; being the evidence of the benefits of clinical pharmacy services by documentation of DRPs; these items can be considered as the advantages (Horvat & Kos, 2016). It is known that the management of critically ill patients is very difficult because of having comorbidities and abrupt changes in organ function. Furthermore, polypharmacy in intensive care units (ICUs) is a cause of adverse drug reactions, complications, and drug-drug interactions (Aljbouri et al. 2013). The study by Tharanon et al. has reported that the too-frequent daily drug order changes, too-frequent use of intravenous drugs, polypharmacy, and multiple organ failure increased the risk of DRPs in ICUs (Tharanon, Putthipokin, & Sakthong, 2022). Studies in the literature have shown that clinical pharmacists in ICUs led to a decrease in the frequency of DRPs, so that the healthcare were improved (Lee et al., 2019; Reinau, Furrer, Stämpfli, Bornand, & Meier, 2019; Tasaka et al., 2018).

In this study, it was aimed to reveal the clinical pharmacist's contribution to patient care in the ICU by determining DRPs, classifying DRPs, and making interventions to solve DRPs. Furthermore, our secondary aim was to determine the risk factors for DRPs in the Internal Diseases ICU.

MATERIALS AND METHODS

This study was conducted at the Internal Diseases ICU of a university hospital between August 16, 2021, and March 16, 2022. In this ICU, patients were hospitalized according to the departments of internal diseases (hematology, nephrology, gastroenterology, endocrinology, and medical oncology). Inclusion criteria were those who were hospitalized in the internal diseases ICU, took at least one drug, and were evaluated by the clinical pharmacist. Inform consent was obtained from all individual participants included in the study or from their relatives. The exclusion criteria were that those patients who were not administered any drug, were younger than 18, weren't evaluated by the clinical pharmacist, or were not approved the patient consent form by the patient or their relatives. Patients' medical therapies were evaluated daily during their stay in hospital. DRPs were being evaluated without any restriction on patients' length of hospital stay. If patients were hospitalized and discharged within the days without the clinical pharmacist, they were not included in the study. DRPs of 257 patients' medical therapy were evaluated prospectively by the clinical pharmacist who was in a clinical pharmacy specialist training program and the interventions were shared with the responsible physician and/or other healthcare staff. Patients were divided into two groups with DRPs and without DRPs. Clinical and demographic characteristics of patients with and without DRPs were recorded. The clinical pharmacist attended clinic visits in the ICU together with the clinicians and the DRPs that had been detected were discussed and determine. Then, the clinical pharmacist followed up the process to see if the problems were resolved. Pharmaceutical Care Network Europe (PCNE) v.9 classification system was utilized to classify these problems. The detected problems that didn't comply with the explanatory categories were classified as the "unclear problem" or "other" problem category. We did not calculate the study size because all patients who met the inclusion criteria between the specified date were evaluated. We included all patients who matched the inclusion criteria during the study period to prevent the probability of bias.

Ethical approval for the study was obtained from the non-interventional ethics committee of İnönü University on 29.06.2021 (Decision no:2021\2267).

Evaluation and Definitions

Sex, age, comorbidity, department of the ICU, clinical features, drugs used before admission, drugs used in the ICU, and daily laboratory data of the patients were recorded on a patient profile form.

Intubation was recorded if the patient was dependent on a mechanical ventilator device for more than 48 hours. The Glasgow coma scale (GCS), which was calculated at the admission of the ICU by clinicians, was recorded. Polypharmacy is defined as the presence of 5 or more drug usage in a patient (Masnoon, Shakib, Kalisch-Ellet, & Caughey, 2017). Fluid and nutrition support and topical dosage forms weren't included in the total number of drugs. The estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulary (Napier et al., 2022). Chronic kidney disease stages, acute kidney injury status, and hemodialysis status were recorded. There were no patients with continuous renal replacement therapy. Appropriateness of dosage regimen and drug-drug interactions were checked with the Lexicomp© drug information database and the interventions were recommended according to Uptodate© and Lexicomp© databases. Only these databases were used to evaluate the patients'medical therapies. Drug-drug interactions that could be the clinical significance were grouped as DRPs and recommendations were made based on them. DRPs and interventions were shared with the responsible physician and/or other healthcare staff. The interventions and status of DRPs were classified by the PCNE v.9 classification system (Pharmaceutical Care Network Europe Association, 2023).

Statistical Analysis

The IBM SPSS (Statistical Package for Social Sciences) 23.0 software program was used for statistical analysis. Normality tests of quantitative data were analyzed by Kolmogorov Smirnov test and were found to be non-normally distributed, so were given as median. Quantitative data from 2 groups were analyzed by Mann Whitney U test. Kruskal-Wallis H test was used for the comparison of quantitative data of >2 groups.

Rates of characteristics and PCNE v9 classification categories were given as numbers and percentages. The relationship of qualitative data between the two groups was determined by the Chi-Square Test. The multivariate analysis was performed using binary logistic regression analysis. The variance explained by the model was shown with the Nagelkerke R2 value. The Hosmer-Lemeshow test was used to show the data fit the model well. The risk factors were explained with the odds ratio. A *p*-value smaller than 0.05 was considered statistically significant.

RESULTS

During the 7 months of study protocol, there were 265 hospitalizations in the ICU and 8 were excluded because of no drug usage. 161 (62.6%) of the patients were male among 257 patients. The patients' median age was 67 and the interquarter range (IQR) was 54-76. Female patients' median age was 66 (IQR: 49-76), and male patients' was 67 (IQR: 56-76.5). The median of the total number of drugs was 10 (IQR: 7-13) for each patient. Patients with DRPs had a significantly higher rate of drug number (median:12, IQR:9-15) than patients without DRPs (median:7, IQR: 5-10) ($p<0.05$). Demographics, GCS, and eGFR were not found in a relationship with the presence of DRPs according to the Mann-Whitney U test ($p>0.05$). The longer hospital stays in the ICU were found to be associated with DRPs detection ($p<0.05$). The mortality rate was significantly higher in patients with DRPs. ($p<0.05$). DRPs detection in hematology and nephrology ICU departments was found significantly higher than in the gastroenterology ICU department ($p<0.05$) (Table 1). 399 DRPs were detected among 257 patients and 399 interventions were made. The number of patients with DRPs was found 157 (61%) and the number of DRPs per patient was found 1.55. The accepted ratio of the interventions was found as 87.5%.

Intubation, polypharmacy, antibacterials, electrolytes, noradrenaline/dopamine, corticosteroids, antifungals, insulin, antivirals, and sedatives/analgesics were found in a link to DRPs detection ($p<0.05$). In multivariate analysis, polypharmacy (OR: 3.955, CI:1.207-11.071) and antibacterials (OR: 3.285, CI: 1.563-6.904) were found to be risk factors for DRPs detection (Table 2).

Comorbidities and their relationship with DRPs detection are given in Table 3. Atrial fibrillation (OR: 2.985, CI: 1.158-7.692) and hematopoietic stem cell transplantation (OR: 3.883, CI: 1.256-11.999) were found to be risk factors for DRPs detection (Table 3).

Treatment safety (P2) (43.4%) was detected to be the most common problem (Table 4). Drug selection (C1) (42.2%) was detected to be the most seen cause of DRPs and dose selection (C3) (41.5%) followed this. The most seen interventions belonged to the "at prescriber level" (I1) (53.4%) category as seen in Table 4. The interventions' accepted status was classified, and the accepted interventions were found by 87.5%. The outcomes of the interventions were classified as not known, solved, partially solved, and not solved as seen in Table 4.

DISCUSSION

Demographic and Clinical Characteristics of Patients

In the study by Albayrak et al., female patients consisted of 37.1% similar to our study (37.4%) (Albayrak, Başgut, Bıkmaz, & Karahalil, 2022). The median age of the patients was found (67), likely to the studies of Albayrak et al. (69) and Ayhan et al. (62.5) (Albayrak et al., 2022; Ayhan, Karakurt, & Sancar, 2022). In our study, the mortality rate was found as 52.1% which differed from the other studies that were found as 77%, 28.7%, and 15% (Albayrak et al., 2022; Ayhan et al., 2022; Johansen, Haustreis, Mowinckel, & Ytrebø, 2016), respectively. We suggested those studies were conducted at different times such as at the new coronavirus disease pandemic season or not, and patients' comorbidities may led to differences of the mortality rates. In the ICU setting studies, there were no relationships between demographics and DRPs detection, similar to our study (Albayrak et al., 2022; Martins, Silva, & Lopes, 2019). In contrast to our study, age is a risk factor for DRPs in a non-ICU setting study, so, this difference could be due to different settings (Lenssen et al., 2016).

We found that the length of hospital stay was significantly higher in patients with DRPs similar to the other ICU setting studies (Albayrak et al., 2022; Martins et al., 2019). Moreover, DRPs detection was found higher in patients with mortality than in discharged patients, similar to the other ICU setting study (Albayrak et al., 2022). In addition, we determined that, DRPs were experienced higher in patients who were ordered antibacterials, antifungals, antivirals, corticosteroids, or sedatives/analgesics. While, the study by Ayhan et al. reported that the presence of antibacterials was found in a relationship with DRPs detection (Ayhan et al., 2022). Furthermore, Greeshma et al. have found that antibacterials and corticosteroids increased the risk of DRPs detection and Martins et al. have reported midazolam to be a risk factor for DRPs detection (Greeshma, Lincy, Maheswari, Tharanath, & Viswam, 2018; Martins et al., 2019).

Polypharmacy was found to be a risk factor for DRPs detection in our study. Similarly, >5 drug usage has also been reported to be a risk factor for DRPs in the literature (Greeshma et al., 2018). A non-ICU setting study has reported that the number of drugs was a risk factor for DRPs (Lenssen et al., 2016). Furthermore, we found that the presence of antibacterials was a risk factor for DRP detection, similar to another ICU setting study (Ayhan et al., 2022).

When we evaluated patients' comorbidities, atrial fibrillation and the history of hematopoietic stem cell transplantation were found to be risk factors for DRPs detection. It was stated in

Table 1. Patient characteristics and their relationship with drug-related problem detection.

Variables	Total (%)	Patients with DRPs n(%)	Patients without DRPs n(%)	*p*
Male	161 (62.6)	99 (63.1)	62 (62)	0.864*
Female	96 (37.4)	58 (36.9)	38 (38)	
Age median (IQR)	67 (54-76)	68 (54-76.5)	66 (55-76)	0.774**
Number of drugs median (IQR)	10 (7-13)	12 (9-15)	7 (5-10)	*<0.001***
GCS median (IQR)	14 (11-15)	13 (11-15)	14 (12-15)	0.227**
eGFR median (IQR)	47 (19-90)	40 (18-76)	50 (23.25-94.75)	0.112**
Length of stay, days median (IQR)	6 (3-11)	8 (4.5-16)	4 (3-7)	*<0.001***
Causes of Leaving the hospital[x]				
Discharge[a]	26 (10.1)	9 (5.7)	17 (17)	*0.01**
Discharge on own responsibility[a,b]	10 (3.9)	7 (4.5)	3 (3)	
Transfer to another service[a,b]	87 (33.9)	50 (31.8)	37 (37)	
Mortality[b]	134 (52.1)	91 (58)	43 (43)	
Departments of the ICU[x]				
Nephrology [b]	79 (30.7)	57(36.3)	22 (22)	*0.002**
Gastroenterology[a]	70 (27.3)	33(21)	37 (37)	
Hematology [b]	59 (23)	43(27.4)	16 (16)	
Medical Oncology [a,b]	43 (16.7)	22(14)	21 (21)	
Endocrinology[a,b]	6 (2.3)	2(1.3)	4 (4)	

[x]The same superscript letters indicate there weren't any differences between groups statistically.
*Pearson Chi-Square test **Mann Whitney U test
Significant values were given in italics.

the literature that clinical pharmacists provide healthcare benefits to patients with these related diseases (Clemmons, 2020; Ritchie, Penson, Akpan, Lip, & Lane, 2022). In a previous study, the number of DRPs per patient was found high in a pediatric hematopoietic stem cell transplantation service which led to the thought that clinical pharmacists have an important role in the management of DRPs in this patient population (Ozdemir, Celiker, Kuskonmaz, Okur, & Cetinkaya, 2019).

The classification of DRPs

The ICU setting studies by Albayrak et al and Martins et al. demonstrated that the mostly reported DRPs are belonged to the P2.1 "adverse drug events (possible) occurring" category by 77.18% and 68.64%, respectively (Albayrak et al., 2022; Martins et al., 2019). Our study showed similarity to these studies as P2.1 was found to be the most common DRPs (43.4%). In contrast to these studies Toukhy et al. have found the P2 category at the rate of 17.5% as the third seen problem while, they found P1 "treatment effectiveness" as the most commonly seen problem by 50.2% (Toukhy, Fayed, Sabry, & Shawki, 2021).

In an ICU setting study by Li X-x et al., the effectiveness of drug therapy (%34.2), the safety of drug therapy (%31.1), and others (%34.7) were detected as categories of DRPs (Li, et al., 2020). In our study, the incidence of the problem categories of DRPs were partially similar to this study in that we found P1 "treatment effectiveness" (26.8%), P2 "treatment safety" (43.4%), and P3 "other" (29.8%). Furthermore, they have reported that adverse drug reactions and concerns about treatment safety stemmed from high drug doses or low drug doses/not frequently enough drug regimens similar to our study (Li, et al., 2020). An ICU setting study by Zaidi et al. reported that unnecessary drug treatment was detected by 37% which differed from our study because of the different DRP classification systems (Zaidi, Hassan, Postma, & Seiw Hain, 2003).

Table 2. Clinical characteristics and drug groups used in the patients, and their relationship with drug-related problem detection.

		Univariate analysis			Multivariate analysis	
Clinical characteristics and used drug groups	**Total n(%)**	**Patients with DRP n(%)**	**Patients without DRP n(%)**	***p***	**OR (CI)**	***p*^x**
Intubation	53 (20.6)	40 (25.5)	13 (13)	*0.016**	0.402 (0.059-2.722)	0.350
Polypharmacy	230 (89.4)	152 (96.8%)	78 (78)	*<0.001**	3.955 (1.207-11.071)	*0.022*
GCS (3-8)	40 (15.6)	27 (17.2)	13 (13)		-	-
GCS (9-13)	88 (34.2)	55 (35)	33 (33)	0.539*	-	-
GCS (14-15)	129 (50.2)	75 (47.8)	54 (54)		-	-
Renal dysfunction	152 (59.14)	98 (62.4)	54 (54)	0.181*	-	-
G3b (GFR<45-30)	5 (1.9)	4 (2.5)	1 (1)		-	-
G4 (GFR<30-15)	11 (4.3)	6 (3.8)	5 (5)	0.4*	-	-
G5 (GFR<15)	4 (1.6)	3 (1.9)	1 (1)		-	-
AKI	92 (35.8)	55 (35)	37 (37)		-	-
AKI on CKD	2 (0.8)	1 (0.6)	1 (1)		-	-
Dialysis	38 (14.8)	29 (18.5)	9 (9)		-	-
Proton pump inhibitors	248 (96.5)	153 (97.5)	95(95)	0.317**	-	-
Antibacterials	207 (80.2)	142 (90.4)	65 (65)	*<0.001**	3.285 (1.563-6.904)	*0.002*
Electrolytes	128 (49.8)	86 (54.8)	42 (42)	*0.046**	0.881 (0.483-1,606)	0.678
Antihypertensives	117 (45.5)	77 (49)	40 (40)	0.156*	-	-
Anticoagulants	106 (41.2)	72 (45.9)	34 (34)	0.06*	-	-
Norepinephrine/dopamine	95 (37)	69 (43.9)	26 (26)	*0.004**	1.514 (0.760-3.017)	0.238
Corticosteroids	71 (27.6)	51 (32.5)	20 (20)	*0.029**	1.397 (0.715-2.730)	0.328
Antifungals	61 (23.7)	49 (31.2)	12 (12)	*<0.001**	1.892 (0.827-4.329)	0.131
Insulin	52 (20.2)	40(25.5)	12 (12)	*0.009**	1.985 (0.925-4.259)	0.058
Sedatives/analgesics	50 (19.5)	39 (24.8)	11 (11)	*0.006**	2.94 (0.332-18.165)	0.379
Antivirals	42 (16.3)	33 (21)	9 (9)	*0.011**	1.483 (0.588-3.740)	0.404
Oral antidiabetics	11 (4.3)	7(4.5)	4 (4)	1**	-	-

*Pearson Chi-Square test **Fischer's Exact test ^xLogistic regression
GCS: Glasgow coma scale, AKI: Acute kidney injury, CKD: Chronic kidney disease, DRP: Drug-related problem, OR: Odds ratio, CI: Confidence interval.
Significant values were given in italics.

Another ICU setting study classified DRPs with a method that consists of 11 categories and found "the drug dose too high" and "unnecessary drug treatment" at rates of 28% and 13%, respectively (Johansen et al., 2016). Our study differed from this study as "the drug dose was too high" and "unnecessary drug treatment" were found at the rates of 10.8% and 24.5%. Although the problems and causes were defined in the PCNE method, only the problems were defined in the classification system used in that study (Johansen et al., 2016).

The most common causes of DRPs were "drug selection" by 42.2% and "dose selection" by 41.5% in our study. Similar to our study, Albayrak et al have reported these categories as the most seen causes of DRPs in the ICU by 40.29% and 54.36% (Albayrak et al., 2022). Furthermore, two different ICU setting studies have reported that the most common causes of DRPs were "drug selection" with 51.1% and 60% according to the PCNE method (Ayhan et al., 2022; Martins et al., 2019). The study by Li X-x et al. found that DRPs mostly stemmed from drug selection (41.3%) and dose selection (29%) (Li et al., 2020). Another ICU setting study found "drug selection" as the most common cause of DRPs at 50.7% and "dose selection" as the third cause at %19.5 (Toukhy, 2021).We determined that C1.3 "no indication for drug" (12%), C1.6 "no or incomplete drug treatment in spite of existing indication" (9%), and C1.2 "inappropriate drug" (8.1%) were the most seen subcategories of C1 "drug selection". In the study by Martins et al., DRPs

Table 3. Frequency of comorbidities and their relationship with drug-related problem (DRP) detection.

		Univariate analysis			Multivariate analysis	
Comorbidity	**Total n(%)**	**Patients with DRP n(%)**	**Patients without DRP n(%)**	***p***	**OR (CI)**	***p*^x**
Hypertension	145 (56.4)	91 (58)	54 (54)	0.532*	-	-
Diabetes	75 (29.2)	42 (26.8)	33 (33)	0.283*	-	-
Solid organ tumor	69 (26.8)	40 (25.5)	29 (29)	0.534*	-	-
Coronary artery disease	62 (24.1)	45 (28.7)	17 (17)	*0.033**	1.743 (0.903-3.367)	0.098
Hematologic malignancy	54 (21)	39 (24.8)	15 (15)	0.059*	-	-
BPH	41 (16)	26 (16.6)	15 (15)	0.739*	-	-
Atrial fibrillation	34 (13.2)	28 (17.8)	6 (6)	*0.006**	2.985 (1.158-7.692)	*0.024**
Cirrhosis	34 (13.2)	20 (12.7)	14 (14)	0.771*	-	-
CP A	2 (0.8)	0	2 (2)	0.350*	-	-
CP B	7 (2.7)	4 (2.5)	3 (3)		-	-
CP C	25 (9.7	16 (10.2)	9 (9)		-	-
COPD	23 (8.9)	15 (9.6)	8 (8)	0.670*	-	-
Hearth failure	23 (8.9)	19 (12.1)	4 (4)	*0.027**	2.275 (0.709-7.3)	0.167
Hematopoietic stem cell transplantation	22 (8.6)	18 (11.5)	4 (4)	*0.037**	3.883 (1.256-11.999)	*0.018**
Vascular disease	19 (7.4)	11 (7)	8 (8)	0.767*	-	-
Cerebrovascular disease	17 (6.6)	15 (9.6)	2 (2)	0.18*	-	-
Epilepsy	17 (6.6)	14 (8.9)	3 (3)	0.109***	-	-
Hypothyroid	14 (5.4)	9(5.7)	5 (5)	0.801*	-	-
Alzheimer's disease	13 (5.05)	9 (5.7)	4 (4)	0.537*	-	-
Asthma	12 (4.7)	8 (5.1)	4 (4)	0.770**	-	-
Autoimmune disease	9 (3.5)	8 (5.1)	1 (1)	0.160**	-	-
Hyperthyroidism	2 (0.8)	1 (0.6)	1 (1)	1**	-	-

*Pearson Chi-Square test **Fischer's Exact test ***Continuity Correction *x*Logistic regression
BPH: Benign prostate hypertrophy, CP: Child pugh, COPD: Chronic obstructive pulmonary disease, DRP: Drug-related problem, OR: Odds ratio, CI: Confidence interval
Significant values were given in italics.

were classified with the PCNE method and C1.6 was found by 6.36%, and C1.2 by 9.09% (Martins et al., 2019). The other ICU setting study reported the conditions that "the drug wasn't given in spite of an existing indication" and "drug was given in spite of no indication" by 33.2% and 14.3% (Al-Jazairi et al., 2008). Contrary categorizing the problems and causes of DRPs in our study, in that study the problems were categorized but the causes of DRPs were not categorized, so this difference may have occurred.

The subcategories of C3 "dose selection"; C3.4 "dosage regimen was too frequent", C3.2 "drug dose too high" and C3.1 "drug dose too low" were found by 15.7%, 10.8%, and 9.5% respectively. Similar to our study, Ayhan et al. have reported C3.2 and C3.1 by 12.4% and 6.2%, respectively (Ayhan et al., 2022). Although similar to our study, Martins et al. found C3.2 by 13.18%, in contrast, they didn't find any DRPs that belong to the C3.4 and C3.1 categories (Martins et al., 2019). In contrast to our study, the study by Albayrak et al. found C3.4, C3.2, and C3.1 by 10.19%, 24.7%, and 14.56% respectively (Albayrak et al., 2022). As seen, there is no linearity in the dose selection of DRPs in the literature and we suggested that this difference may stem from the clinicians' ordering practice. C6.1 "inappropriate timing of administration and dosing intervals" was found the most and only seen subcategory of C6 and showed similarity to the other ICU setting studies (Albayrak et al., 2022; Martins et al., 2019). We found that most of the interventions were made at I1 "at the prescriber level" and I3 "at drug level" category, similar to the other three ICU setting studies (Albayrak et al., 2022; Ayhan et al., 2022; Martins et al., 2019). We found I1.3 "intervention proposed to the prescriber" had a higher rate than the I1.4 "intervention discussed to the prescriber" similar to the other two ICU setting studies (Albayrak et al., 2022; Martins et al., 2019). Toukhy et al. have reported that I1 "at the prescriber level" and I3 "at drug level" categories by 57.4% and 40% as the most made interventions in the ICU, similarly the rates were 53.4% and 44.6% in our study (Toukhy et al., 2021).

Table 4. The classification of the drug-related problems and planned interventions.

The problems	**n (%)**
P1 Treatment effectiveness	107 (26.8)
P1.1. No effect of drug treatment	4 (1)
P1.2. Effect of drug treatment not optimal	67 (16.8)
P1.3. Untreated symptoms or indication	36 (9)
P2 Treatment safety	173 (43.4)
P2.1. Adverse drug (possibly) occurring	173 (43.4)
P3 Other	119 (29.8)
P3.1. Problem with cost-effectiveness of the treatment	2 (0.5)
P3.2. Unnecessary drug-treatment	98 (24.5)
P3.3. Unclear problem/complaint. Further clarification necessary	19 (4.8)
The causes	**n (%)**
C1 Drug selection	183 (42.2)
C1.1. Inappropriate drug according to guidelines/formulary	10 (2.3)
C1.2. Inappropriate drug (within guidelines but otherwise contraindicated)	35 (8.1)
C1.3. No indication for drug	52 (12)
C1.4. Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	7 (1.6)
C1.5. Inappropriate duplication of therapeutic group or active ingredient	33 (7.6)
C1.6. No or incomplete drug treatment in spite of existing indication	39 (9)
C1.7. Too many drugs prescribed for indication	7 (1.6)
C2 Drug form	14 (3.2)
C2.1. Inappropriate drug form (for this patient)	14 (3.2)
C3 Dose selection	180 (41.5)
C3.1. Drug dose too low	41 (9.5)
C3.2. Drug dose too high	47 (10.8)
C3.3. Dosage regimen not frequent enough	24 (5.5)
C3.4. Dosage regimen too frequent	68 (15.7)
C4 Treatment duration	8 (1.8)
C4.2. Duration of treatment too long	8 (1.8)
C6 Drug use process	11 (2.5)
C6.1. Inappropriate timing of administration or dosing intervals	6 (1.4)
C6.2. Drug under-administered	2 (0.5)
C6.3. Drug over-administered	1 (0.2)
C6.4. Drug not administered at all	1(0.2)
C6.5 Wrong drug administered	1(0.2)
C9 Other	38 (8.8)
C9.1. No or inappropriate outcome monitoring	15 (3.5)
C9.2. Other cause; specify	21 (4.8)
C9.3. No obvious cause	2 (0.5)
The planned interventions	**n (%)**
I1 At prescriber level	398 (53.4)

Table 4. The classification of the drug-related problems and planned interventions. (Continued)

I1.3. Intervention proposed to prescriber	396 (53.1)
I1.4. Intervention discussed with prescriber	2 (0.3)
I3 At drug level	332 (44.6)
I3.1. Drug changed to …	12 (1.6)
I3.2. Dosage changed to …	145 (19.5)
I3.3. Formulation changed to …	4 (0.5)
I3.4. Instructions for use changed to …	8 (1.1)
I3.5. Drug paused or stopped	131 (17.6)
I3.6. Drug started	32 (4.3)
I4 Other intervention or activity	15 (2)
I4.1. Other intervention (specify)	15 (2)
Acceptance of the intervention proposals	**n (%)**
A1 Intervention accepted	349 (87.5)
A1.1. Intervention accepted and fully implemented	348 (87.2)
A1.2. Intervention accepted, partially implemented	1 (0.3)
A2 Intervention not accepted	50 (12.5)
A2.1. Intervention not accepted: not feasible	1 (0.25)
A2.2. Intervention not accepted: no agreement	49 (12.3)
Status of the DRP	**n (%)**
O1 Problem totally solved	348 (87.2)
O2 Problem partially solved	2 (0.5)
O3 Not solved	49 (12.3)
O3.2. Problem not solved, lack of cooperation of prescriber	48 (12)
O3.4. No need or possibility to solve problem	1 (0.3)

In the current study, the most seen planned interventions' subcategory of I3, was found I3.2 "dosage changed to . . . " by 19.5%. Similar to our study, Martins et al. have reported the I3.2 by 24.09% as the most seen subcategory of the I3 category (Martins et al., 2019). In contrast to our study, Al-Azzam et al. classified only the interventions and found the interventions about drug dose changes by 7.3% (Al-azzam, Shara, Alzoubi, Almahasneh, & Iflaifel, 2013). It was reported in the study by Bourne et al. that the most made interventions were "new drug addiction", "drug dose change", "drug administration changes", and "stopping the drug", respectively (Bourne, Choo, & Dorwarb, 2014). We thought that these differences originated from the different drug classification systems. The I3.6 "drug started" subcategory was found by 4.3% in our study which differed from the study by Jiang et al. (16.6%), and Kubas and Halboup (18.9%) (Jiang, Chen, Zhang, Lu & Zhao, 2014; Kubas & Halboup, 2020). We thought that these differences occurred since the classification systems differed from each other and our study.

The accepted interventions were found at the rate of 87.5% in our study, similar to other ICU setting studies that were found by Albayrak et al. (90.8%), Johansen et al (87%), and Martins et al. (85.45%) (Albayrak et al., 2022; Johansen et al., 2016; Martins et al., 2019). It is possible to say that clinical pharmacist interventions' were accepted at a higher rate independent of the studies' geography. The number of DRPs per patient was found (1.55) similar to other studies in the literature that were found as 1.8 and 1.36 (Johansen et al., 2016; Albayrak et al., 2022; Martins et al., 2019).

Polymorbidity, polypharmacy, and anticoagulant, antibacterial, and corticosteroid usage were found to be risk factors for DRPs (Kaufman et al., 2015). Polypharmacy and antibacterial usage were found to be risk factors in our study harmoniously with the literature. Differently, atrial fibrillation and hematopoietic stem cell transplantation were found to be independent risk factors for DRPs among comorbidities. Clinicians should pay attention when prescribing new drugs to patients with atrial fibrillation and a history of hematopoietic stem cell transplantation. Furthermore, clinicians and clinical pharmacists should pay attention if polypharmacy and antibacterial drugs are present in medical therapy.

DRPs are seen commonly in ICUs and clinical pharmacists

recommend solution proposals to clinicians. In the literature treatment safety was the most seen DRPs category, and drug selection and dose selection were the most seen causes of DRPs (Albayrak et al., 2022; Ayhan et al., 2022; Martins et al., 2019).

The most commonly seen DRP categories (treatment safety) and their causes (drug selection and dose selection) were found similar to the literature, so clinical pharmacists and clinicians should pay attention to these topics. The literature and our study promote clinical pharmacists' beneficial roles in ICUs as well as all services of hospitals. We thought that one or more clinical pharmacists should work in all services of hospitals, especially in ICUs so the World's healthcare system will take an important step. In the literature, there are many studies about the evaluation of the clinical pharmacist's implementation in the ICUs. However, this study is one of the most comprehensive studies among a few studies which were conducted in internal diseases ICUs. New studies should be done in specific departments of internal diseases ICUs (Nephrology, Gastroenterology, Endocrinology, Hematology, Medical Oncology, etc.)

Strengths and Limitations

The limitations of our study were being one single-center study, not specifying an ICU department, and evaluation of DRPs by one clinical pharmacist; and while inclusion criteria were determined to prevent potential bias, the homogeneity of the study might have not been achieved. Additionally, we could count as a limitation that some DRPs did not comply with the explanatory categories of the PCNE method, so they were classified under the "unclear problem" of the "other" problem category. The strengths of our study were having a prospective design, a large patient population for 7 months, and a comparison of different science departments in the ICU.

CONCLUSION

Atrial fibrillation and hematopoietic stem cell transplantation were found to be independent risk factors for DRPs among comorbidities offering new data to the literature. The presence of antibacterials and polypharmacy were found to be independent risk factors for DRPs as supporting to the literature.

The most common DRP categories (treatment safety) and their causes (drug selection and dose selection) were found similar to the other studies, thus, supporting the literature.

It was concluded in this study that; clinicians should pay attention when prescribing new drugs to patients with atrial fibrillation and a history of hematopoietic stem cell transplantation. Clinical pharmacists and clinicians should pay attention to "drug selection" and "dose selection" areas when reviewing patients' therapy in ICUs. Furthermore, this study attracts attention to the evaluation of clinical pharmacy services in specific areas of internal diseases ICUs.

The literature and our study promote clinical pharmacists' beneficial roles in ICUs as well as in all services of hospitals. We suggest that one or more clinical pharmacists should work in all services of hospitals, especially in ICUs.

List of Abbreviations

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
DRP: Drug-related problem
eGFR: estimated glomerular filtration rate.
GCS: Glasgow coma scale
ICU: Intensive care unit
PCNE: Pharmaceutical Care Network Europe

Ethics Committee Approval: Ethical approval for the study was obtained from the non-interventional ethics committee of İnönü University on 29.06.2021 (Decision no:2021267).

Informed Consent: Inform consent was obtained from all individual participants included in the study or from their relatives.

Peer-review: Externally peer-reviewed.

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