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Evaluation of drug-related problems of intensive care unit patients by clinical pharmacists: a retrospective longitudinal study

Short Title: Drug-related problems of critically ill patients

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ABSTRACT
Objectives
The goal of this study is to identify drug-related problems (DRPs) and risk factors associated with the emergence of DRPs in intensive care unit (ICU) patients. In addition, it was aimed to enlighten pharmacists who are considering specializing in the critical care pharmacy field in the future.
Methods
This retrospective longitudinal study was performed in the anaesthesiology and reanimation ICU of a university-affiliated tertiary care hospital. Identified DRPs by clinical pharmacists were classified by the Pharmaceutical Care Network Europe Classification for DRPs, v9.1. The DRPs, the relationship between various patient-related factors and risk factors associated with the emergence of DRPs are examined through statistical analysis.
Results
In total, 222 patients were included in the study 128 (57.7%) of which were male. DRP count was 388 in 135 of patients (1.75 ± 2.47 DRPs per patient). In group in which at least 1 DRP identified, the duration of hospitalization was longer than the group in which no DRP identified (p<0.001). In groups in which there was the presence of mechanical ventilation support at admission or mortality, the mean DRP count was significantly higher than the other group (p<0.05). Age, duration of hospitalization, and the Acute Physiology and Chronic Health Evaluation II score at admission had positive relationships with the drug-related problem count, but the Glasgow Coma Scale shows a negative relationship (p<0.05). According to the binary logistic regression analysis, in which the age of the patient, the Glasgow Coma Scale score, the Acute Physiology and Chronic Health Evaluation II score at admission, the duration of hospitalization, and the presence of mechanical ventilation support at admission were included, only the Acute Physiology and Chronic Health Evaluation II score at admission and the duration of hospitalization have significantly affected the emergence of DRPs. The major problem was related to the treatment effectiveness (47.9%) and it was followed by treatment safety problems (29.9%). These problems' major causes were dose selection (44.0%) and drug selection (36.8). The interventions made at drug level (97.2%) and prescriber level (2.3%). The acceptance rate of interventions and the resolution rate of the DRPs was found as 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 detect and treat DRPs quickly. Our analysis shows that clinical pharmacy services are needed in high-drug-related problem 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 could be classified as DRPs. [2] DRPs and ADEs are frequently encountered in intensive care units (ICUs).[3] The treatments administered to the 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 the DRPs and ADEs.[5] A systematic review done in 2007 shows that 46.5% of the ADEs are preventable, and 16.0% of these are emerging from medication errors.[6] There are studies that include pharmacists' interventions done 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] We believe that through the integration of clinical pharmacists into the existing healthcare system, it will be possible to better detect and tackle DRPs.

The goal of this study is to identify DRPs and risk factors associated with the emergence of DRPs in ICU patients. In addition, it was aimed to enlighten pharmacists who are considering specializing in the critical care pharmacy field in the future.

METHODS

Study Design and Setting

The current retrospective longitudinal study was carried out 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 doctors. Specialists and resident physicians also work alternately. The working hours are between 8 a.m. and 5 p.m. in the ICU. Two clinical pharmacy residents joined the rounds on weekdays with ICU and infectious diseases physicians, nurses, and technicians. The recommendations for DRPs made by the clinical pharmacy residents were recorded and then examined along with various factors. The classification of the DRPs according to the PCNE classification system was done by reaching a consensus among clinical pharmacy residents.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Inonu University (April 11, 2023/4521). The participation consent was granted from all patients included in the study.

Participants

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

Outcomes

The primary outcomes of this study are determining DRPs, the acceptance rates of the interventions, and resolution rate of DRPs by clinical pharmacists in the ICU. The secondary outcomes of this study are determining the medication errors that cause DRP the most frequently, as well as the severity of those errors and determining the relationship between DRPs and various patient-related factors.

Data Collection

The hospital's electronic database was used to get information about the patients' demographics, diagnoses, laboratory results, Glasgow Coma Scale (GCS) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores at admission, duration of hospitalization, status of mechanical ventilation support at admission, and types of admission. Daily medication charts were accessed 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. UpToDate®, Micromedex®, Lexicomp®, Sanford Antimicrobial Guide®, CredibleMeds®, and LiverTox® databases were used in identifying DRPs. Identified DRPs were classified using the PCNE Classification for Drug-Related Problems, v9.1. In addition, DRPs were classified using the National Coordinating Council for Medication Error Reporting and Prevention, revised in October 2022 (NCC MERP) Index to see to what extent patients were harmed.

Statistical Analysis

Statistical analysis was performed using 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 seen that none of the data was distributed normally, so non-parametric tests were applied. Continuous and categorical data were presented as median [25th percentile – 75th percentile] and number (percentage), respectively. There were no missing data in the study. While comparison of the continuous data between the two groups was made using the Mann-Whitney U test, categorical data was compared using Fisher's exact test. Whether there is an association between the two continuous variables was explored using Spearman's correlation test. The correlation coefficient value was interpretated as follows: Correlation coefficient<0.3 was interpretated as poor, correlation coefficient 0.3 to 0.5 was interpretated as fair, correlation coefficient 0.6 up to 0.8 was interpretated as moderately strong, and correlation coefficient≥0.8 was interpretated as very strong linear relationship.[11] A binary logistic regression analysis was performed to examine the extent to which various patient-related factors have an effect on the emergence of DRP. A p value smaller than 0.05 is considered statistically significant.

RESULTS

In the study period, 418 patients were admitted to the ICU. The 196 of the patients 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 which 57.7% were male. One or more DRPs were identified in 135 patients, for a total of 388 DRPs (1.75 ± 2.47 DRPs per patient). Total

patient days were determined to be 4,868 (79.7 DRPs per 1000 patient days). The characteristics of the patients are given in Table 1.
The top 4 admission diagnoses classified according to the ICD-10 were as follows: I60 Subarachnoid Haemorrhage 15 (6.8%), A41.9 Sepsis 13 (5.9%), J15.9 Bacterial Pneumoniae 12 (5.4%), and V49.9 Car Occupant [Any] Injured in Unspecified Traffic Accident 12 (5.4%).
The DRP counts were compared based on the presence of mechanical ventilation support, mortality, and the presence of surgery and are given in Table 2.
The relationship between DRP count and duration of hospitalization, age, GCS at admission, and APACHE II score at admission was investigated to establish whether or not there was a correlation and, if so, to what extent. The output of the correlation analysis is given in Table 3.
On the basis of a binary logistic regression, the effects of age, GCS at admission, APACHE II score at admission, duration of hospitalization, and presence of mechanical ventilation support at admission on the likelihood of patients having DRP were determined. Statistically, the logistic regression model was significant, $\chi2(5) = 42.132$, $p < 0.001$. The Hosmer-Lemeshow test has showed that the data fit the model well, $\chi2(8) = 12.579$, $p = 0.127$. The model accurately identified 73.9% of the cases and explained 23.4% (Nagelkerke R^2) of the variance in emergence of DRP. An increase of 1 unit in the APACHE II score at admission and the duration of hospitalization increases 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 at admission, and the presence of mechanical ventilation support at admission did not have a statistically significant effect on the likelihood of the emergence of DRP.
The DRPs were classified according to the NCC MERP Index in an attempt to visualise harm status and the results are given in Table 4.
The DRPs were classified according to the PCNE v9.1, of which 205 (52.8%) were potential DRPs and 183 (47.2%) were manifest DRPs. Among manifest DRPs, 168 (91.80%) of them were accepted and 153 (83.61%) of them were solved. Pertaining results are given in Table 5.
According to the ATC classification system, the first three classes most closely related to DRPs were as follows: 104 (26.8%) Antibacterials for Systemic Use, 45 (11.6%) General Nutrients, and 25 (6.4%) I.V. Solution Additives. Meropenem (24, 23.1%), colistin (20, 19.2%), and piperacillin-tazobactam (13, 12.5%) were the top three antibacterial medications that were most closely associated with DRPs. In total, 116 DRPs were identified concerning possible ADEs. The first three drugs for which interventions were made in apprehensive of possible ADEs were meropenem (14, 12.1%), colistin (13, 11.2%), and piperacillin-tazobactam (9, 7.8%). The sample clinical pharmacist interventions are given in Table 6.

DISCUSSION

To the best of our knowledge, this is the first DRP study to have been performed in the anaesthesiology and reanimation ICU of a tertiary care hospital in Türkiye that included clinical pharmacists' interventions in the resolution of DRPs.
Since clinical pharmacy specialization is a new health care profession in Türkiye, this study is important to enlighten pharmacists who are considering specializing in the critical care pharmacy field in the future.
This study has a number of strengths, one of which is that the PCNE classification is determined by reaching a consensus between two clinical pharmacists, which helps to reduce the possibility of bias. Another strength is that it classifies DRPs that occur in ICUs, provides recommendations for the management of DRPs, and classifies the severity of medication errors by using the NCC MERP. Besides, the current 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 per patient [12]. In another study, 69.8% of patients had at least one DRP, and the average DRP counts 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 the patients, and the DRP counts 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 found to be higher due to the inability of critically ill patients in the ICU to continue their medications they use at home. At the same time, the fact that the intensive care team where the study was conducted was not familiar with the clinical pharmacist recommendations is one of the factors affecting the detected DRP numbers.[15]
In our study, the mean DRP counts seen in the group receiving mechanical ventilation support was found to be significantly higher 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 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 indicate that the patient's condition is more critical. Due to the complexity of pharmacotherapy in such patients, extra attention is required in terms of DRPs. According to our findings, the mean APACHE II score was found to be higher and the GCS was found to be lower 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 prone to 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] Due to such changes, the incidence of DRP in critically ill patients may be higher than in the general population. In a study examining the causes of DRPs, it was determined that C1-drug selection (41.3%) and C3-dose 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-dose selection (44.0%) and C1-drug selection (36.8%) associated DRPs were found to be 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 the pharmacist taking part in the 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 in geriatric [23] and neurological [24] patients, I1-at prescriber level interventions had the highest rate. In our study, the majority of interventions were performed at the I3-drug level (97.1%). We think that the biggest reason for the difference is that physicians in the service, especially infectious disease specialists, allow clinical pharmacists to make changes in adjusting the doses of drugs.

It has been observed that the acceptance rate of recommendations in previous studies is over 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 DRPs were completely resolved, which is in line with those in the literature.

In a study, antibiotics were found to be the drug group causing the most DRP, followed by antiplatelet drugs and PPIs.[29] In another study, the most common drug groups causing DRP were found to be antihypertensive drugs, antithrombotic drugs, and statins.[30] In our study, the most common drug groups causing DRP were antibacterials for systemic use (26.8%), general nutrients (11.6%), and I.V. 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 very frequent renal dose adjustment.

In many studies, each DRP was graded using the NCC MERP, 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, and 45.9% were in category B, 41.5% were in category C, and 12.7% were in category D.[33] In our study, the distribution of DRPs according to the NCC MERP was found to be 52.8% in category A, 36.1% in category D, 5.3% in category E, and 5.4% in category F. The temporary harms were detected early, and necessary interventions were made by clinical pharmacists so that these harms could not be converted to permanent harm later. This difference across the studies may stem from the nature of the place where health care is provided and the diversity of the patient profiles.

In a study conducted in the internal medicine ward in Türkiye, a positive-oriented fair (r= 0.411) relationship was found between the DRP counts and age, and a positive-oriented fair (r= 0.302) relationship between the DRP counts and the length of stay in the hospital.[34] In this study, the DRP counts had a positive-oriented poor (r= 0.133) association with age and a positive-oriented fair (r= 0.446) association with duration of hospitalization. Changes in pharmacokinetics and pharmacodynamics associated with aging can be noticed in geriatric patients, which explains why this patient population has a higher incidence of DRPs. On the other side, 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 elderly patients were included, the multivariate analysis showed that the length of stay increases 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, it was seen that the length of stay had no significant effect on the presence of DRP (p>0.05).[13] Albeit, in our study, it was shown that the duration of hospitalization increased the presence of DRP by 1.042 times (p<0.05). This difference across the aforementioned studies may arise from the diversity of sample sizes. Martins[13] *et al.* 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 performed to obtain more generalizable results in which a larger number of patients are included and more than one centre is included. More advanced research should be done on risk factors associated with the emergence of DRPs to inform healthcare providers. In addition, more studies are needed to show the impact of clinical pharmacy services in different areas of the health system, especially in ICUs.

STUDY LIMITATIONS

One of the limitations of the study was that it was only carried out in a single centre with a relatively small number of patients overall. The DRP counts that are identified may be lower than it actually is because clinical pharmacists were absent from the ward on weekends and holidays. The other limitation is the lack of a cost-benefit analysis to defend the role of the clinical pharmacist.

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 solution by making suggestions for DRPs in line with the current literature. Our study has shown that clinical pharmacy services are necessary and should be applied in wards such as ICUs where the rate of DRPs may be high.

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REFERENCES

1. Mil JWFv, Horvat N, Westerlund T, Richling I. PCNE Classification for Drug-Related Problems V9.1 [online]. 2020 [Available from: https://www.pcne.org/upload/files/417_PCNE_classification_V9-1_final.pdf accessed 03 Apr 2023.
2. Maslub MG, Radwan MA, Mikhail MS, Abdalla ZA, Youssef YL, Abdal Hafiz AI, Zain Eldien KM, Sha'aban A. Assessment of the latest prescribed drug-related problems. Eur Rev Med Pharmacol Sci. 2022;26:2373-2387.
3. Rothschild JM, Landrigan CP, Cronin JW, Kaushal R, Lockley SW, Burdick E, Stone PH, Lilly CM, Katz JT, Czeisler CA, Bates DW. The Critical Care Safety Study: The incidence and nature of adverse events and serious medical errors in intensive care. Crit Care Med. 2005;33:1694-1700.
4. Bell CM, Brener SS, Gunraj N, Huo C, Bierman AS, Scales DC, Bajcar J, Zwarenstein M, Urbach DR. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. JAMA. 2011;306:840-847.
5. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, Group HS. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168:1890-1896.
6. Krahenbuhl-Melcher A, Schlienger R, Lampert M, Haschke M, Drewe J, Krahenbuhl S. Drug-related problems in hospitals: a review of the recent literature. Drug Saf. 2007;30:379-407.
7. Tharanon V, Putthipokin K, Sakthong P. Drug-related problems identified during pharmaceutical care interventions in an intensive care unit at a tertiary university hospital. SAGE Open Med. 2022;10:20503121221090881.
8. Howle LM, Kirkpatrick CMJ, Trethewy CE. Clinical pharmacy in a regional Australian intensive care unit. J Pharm Pract Res. 2018;48:36-43.
9. Chiang LH, Huang YL, Tsai TC. Clinical pharmacy interventions in intensive care unit patients. J Clin Pharm Ther. 2021;46:128-133.
10. Bremer S, Henjum S, Saether EM, Hovland R. Drug-related problems and satisfaction among patients receiving pharmacist-led consultations at the initiation of cardiovascular drugs. Res Social Adm Pharm. 2022;18:3939-3947.
11. Chan YH. Biostatistics 104: correlational analysis. Singapore Med J. 2003;44:614-619.
12. Albayrak A, Basgut B, Bikmaz GA, Karahalil B. Clinical pharmacist assessment of drug-related problems among intensive care unit patients in a Turkish university hospital. BMC Health Serv Res. 2022;22:79.
13. Martins RR, Silva LT, Lopes FM. Impact of medication therapy management on pharmacotherapy safety in an intensive care unit. Int J Clin Pharm. 2019;41:179-188.
14. Amankwa Harrison M, Marfo AFA, Buabeng KO, Nkansah FA, Boateng DP, Ankrah DNA. Drug-related problems among hospitalized hypertensive and heart failure patients and physician acceptance of pharmacists' interventions at a teaching hospital in Ghana. Health Sci Rep. 2022;5:e786.
15. Jiang SP, Chen J, Zhang XG, Lu XY, Zhao QW. Implementation of pharmacists' interventions and assessment of medication errors in an intensive care unit of a Chinese tertiary hospital. Ther Clin Risk Manag. 2014;10:861-866.
16. Ayhan YE, Karakurt S, Sancar M. The effect of the clinical pharmacist in minimizing drug-related problems and related costs in the intensive care unit in Turkey: A non-randomized controlled study. J Clin Pharm Ther. 2022;47:1867-1874.
17. Kane-Gill SL, Kowiatek JG, Weber RJ. A comparison of voluntarily reported medication errors in intensive care and general care units. Qual Saf Health Care. 2010;19:55-59.

18. Kane-Gill SL, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients*. Crit Care Med. 2012;40:823-828.
19. Li XX, Zheng SQ, Gu JH, Huang T, Liu F, Ge QG, Liu B, Li C, Yi M, Qin YF, Zhao RS, Shi LW. Drug-Related Problems Identified During Pharmacy Intervention and Consultation: Implementation of an Intensive Care Unit Pharmaceutical Care Model. Front Pharmacol. 2020;11:571906.
20. Leopoldino RD, Santos MT, Costa TX, Martins RR, Oliveira AG. Drug related problems in the neonatal intensive care unit: incidence, characterization and clinical relevance. BMC Pediatr. 2019;19:134.
21. Liu XX, Wang HX, Hu YY, Zhu XT, Tan X, Yang Y, Hang YF, Zhu JG. Drug-related problems identified by clinical pharmacists in nephrology department of a tertiary hospital in China-a single center study. Ann Palliat Med. 2021;10:8701-8708.
22. Agnol RD, Dos Santos MT, Michalowski MB, Einsfeld L. Pharmacists' interventions on 2 years of drug monitoring in an oncology pediatric inpatient ward. J Oncol Pharm Pract. 2022;28:1754-1762.
23. Ma Z, Sun S, Zhang C, Yuan X, Chen Q, Wu J, Wang X, Liu L. Characteristics of drug-related problems and pharmacists' interventions in a geriatric unit in China. Int J Clin Pharm. 2021;43:270-274.
24. Ali MAS, Khedr EMH, Ahmed FAH, Mohamed NNE. Clinical pharmacist interventions in managing drug-related problems in hospitalized patients with neurological diseases. Int J Clin Pharm. 2018;40:1257-1264.
25. Hailu BY, Berhe DF, Gudina EK, Gidey K, Getachew M. Drug related problems in admitted geriatric patients: the impact of clinical pharmacist interventions. BMC Geriatr. 2020;20:13.
26. Iqbal MJ, Mohammad Ishaq G, Assiri AA. Connecting Pharmacists and Other Health Care Providers (HCPs) towards Drug Therapy Optimization: A Pharmaceutical Care Approach. Int J Clin Pract. 2023;2023:3336736.
27. Tan BK, Chua SS, Chen LC, Chang KM, Balashanker S, Bee PC. Acceptability of pharmacist-led interventions to resolve drug-related problems in patients with chronic myeloid leukaemia. J Oncol Pharm Pract. 2021;27:1644-1656.
28. Bosnak AS, Birand N, Diker O, Abdi A, Basgut B. The role of the pharmacist in the multidisciplinary approach to the prevention and resolution of drug-related problems in cancer chemotherapy. J Oncol Pharm Pract. 2019;25:1312-1320.
29. Babelghaith SD, Wajid S, Alrabiah Z, Othiq MAM, Alghadeer S, Alhossan A, Al-Arifi M, Attafi IM. Drug-Related Problems and Pharmacist Intervention at a General Hospital in the Jazan Region, Saudi Arabia. Risk Manag Healthc Policy. 2020;13:373-378.
30. Semcharoen K, Supornpun S, Nathisuwan S, Kongwatcharapong J. Characteristic of drug-related problems and pharmacists' interventions in a stroke unit in Thailand. Int J Clin Pharm. 2019;41:880-887.
31. Belaiche S, Goulois S, DeBerranger E, Odou P, Balagny S, Decaudin B. Clinical pharmacist and pharmaceutical interventions in HBH unit: a French observational study. Acta Clin Belg. 2021;76:258-263.
32. Hartwig SC, Denger SD, Schneider PJ. Severity-indexed, incident report-based medication error-reporting program. Am J Hosp Pharm. 1991;48:2611-2616.
33. Deawjaroen K, Sillabutra J, Poolsup N, Stewart D, Suksomboon N. Characteristics of drug-related problems and pharmacist's interventions in hospitalized patients in Thailand: a prospective observational study. Sci Rep. 2022;12:17107.
34. Abunahlah N, Elawaisi A, Velibeyoglu FM, Sancar M. Drug related problems identified by clinical pharmacist at the Internal Medicine Ward in Turkey. Int J Clin Pharm. 2018;40:360-367.

TABLES

Table 1 The characteristics of the patients

Characteristic	Total	DRPs identified	No DRPs identified	*p*
Patients (n, %)	222 (100.0)	135 (60.8)	87 (39.2)	
Gender (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 at 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, %)				0.003[a]
Emergency	90 (40.5)	44 (32.6)	46 (52.9)	
Another ward/hospital	132 (59.5)	91 (67.4)	41 (47.1)	
CRP value at admission (upper limit of normal* is 0.351 mg/dL) (n, %)				0.376[a]
Normal	41 (18.5)	22 (16.3)	19 (21.8)	
High	181 (81.5)	113 (83.7)	68 (78.2)	
PCT value at admission (upper limit of normal* is 0.5 ng/mL) (n, %)				0.073[a]
Normal	98 (44.1)	53 (39.3)	45 (51.7)	
High	124 (55.9)	82 (60.7)	42 (48.3)	
SCr value at admission (upper limit of normal* is 1.25 mg/dL) (n, %)				0,130[a]
Normal	118 (53.2)	66 (48.9)	52 (59.8)	
High	104 (46.9)	69 (51.1)	35 (40.2)	

APACHE II: Acute Physiology and Chronic Health Evaluation II, CRP: C-reactive Protein, GCS: Glasgow Coma Scale, PCT: Procalcitonin, SCr: Serum Creatinine

[a] Fisher's Exact test, [b] Mann-Whitney U test

* The upper limit of normal values has been obtained from the hospital's laboratory results.

Table 2 The comparison of means of DRP counts according to the various patient-related factors

Factor	Total (mean ± standard deviation)	Yes (mean ± standard deviation)	No (mean ± standard deviation)	*p*
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				

Table 3 The relationship between various patient-related characteristics and DRP count

Patient Characteristics	Spearman's Rho	Orientation and Degree of Association	*p*
Duration of hospitalization	0.446	Positive oriented fair	<0.001
Age	0.133	Positive oriented poor	0.048
GCS at admission	-0.302	Negative oriented fair	<0.001
APACHE II score at admission	0.308	Positive oriented fair	<0.001
APACHE II: Acute Physiology and Chronic Health Evaluation II, GCS: Glasgow Coma Scale			

Table 4 The distribution of DRPs according to the NCC MERP index

Category	Explanation	n (%)	Harm Status, n (%)
A	Circumstances or events that have the capacity to cause error	205 (52.8)	No Error, 205 (52.8)
B	An error occurred but the error 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 required intervention to preclude harm	140 (36.1)	
E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention	20 (5.2)	Error, Harm, 41 (10.6)
F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization	21 (5.4)	

Table 5 The classification of the DRPs according to the PCNE classification system v9.1

Domains	Code	Sub Domains	n (%)
Problems			388 (100.0)
Treatment effectiveness			186 (47.9)
	P1.3	Untreated symptoms or indication	95 (24.5)
	P1.2	Effect of drug treatment not optimal	90 (23.2)
	P1.1	No effect of drug treatment despite correct use	1 (0.3)
Treatment Safety			116 (29.9)
	P2.1	Adverse drug event (possibly) 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 too high	59 (14.1)
	C3.1	Drug dose too low	55 (13.2)
	C3.4	Dosage regimen too frequent	46 (11.0)
	C3.3	Dosage regimen not frequent enough	22 (5.3)
	C3.5	Dose timing instructions wrong, 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 drug	26 (6.2)
	C1.3	Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	15 (3.6)
	C1.4	Inappropriate duplication of therapeutic group or active ingredient	11 (2.6)
	C1.1	Inappropriate drug according to guidelines/formulary	3 (0.7)
	C1.6	Too many different drugs/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	Duration of treatment too long	34 (8.1)
Patient transfer related			4 (1.0)
	C8.1	Medication reconciliation problem	4 (1.0)
Drug form			2 (0.5)
	C2.1	Inappropriate drug form/formulation (for this patient)	2 (0.5)
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 administered via wrong route by a health professional	1 (0.2)
Planned Interventions			388 (100.0)
At drug level			377 (97.2)
	I3.2	Dosage changed to …	171 (44.1)
	I3.6	Drug started	101 (26.0)
	I3.5	Drug paused or stopped	77 (19.9)
	I3.1	Drug changed to …	19 (4.9)

	I3.4	Instructions for use changed to …	7 (1.8)
	I3.3	Formulation changed to …	2 (0.5)
At prescriber level			11 (2.8)
	I1.3	Intervention proposed to prescriber	9 (2.3)
	I1.1	Prescriber 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)
Status of the DRP			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 cooperation of prescriber	21 (5.4)
	O3.4	No need or possibility to solve problem	7 (1.8)
	O3.3	Problem not solved; intervention not effective	4 (1.0)
Not known			22 (5.7)
	O0.1	Problem status unknown	22 (5.7)
Partially solved			4 (1.0)
	O2.1	Problem partially solved	4 (1.0)

Table 6 The sample pharmacist interventions at drug and DRP cause levels

Cause	Drug	Pharmacist Intervention
Dose selection		
C3.2 Drug dose of a single active ingredient too high	Piperacillin-tazobactam	The patient was being administered 4.5 g q6h piperacillin-tazobactam in spite of haemodialysis therapy. The pharmacist recommended changing the dosage of the drug to 2.25 g q6h.
C3.1 Drug dose too low	Valproic acid	The patient was being administered valproic acid 500 mg q12h and serum valproic acid level of the patient was 29 mg/L. The pharmacist recommended changing the dosage of the drug to 500 mg q8h.
C3.4 Dosage regimen too frequent	Pantoprazole	The patient was being administered intravenous pantoprazole 40 mg q12h in spite of no gastrointestinal bleeding signs. The pharmacist recommended changing the dosage of the drug to 40 mg q24h.
C3.3 Dosage regimen not frequent enough	Meropenem	The patient was being administered 1 g q12h meropenem in spite of no renal impairment. The pharmacist recommended changing the dosage of the drug to 1 g q8h.
C3.5 Dose timing instructions wrong, unclear or missing	Meropenem	The patient was being administered 30 minutes of meropenem infusion therapy in spite of the presence of microorganism resistance. The pharmacist recommended increasing the duration of the infusion to 3 hours.
Drug selection		
C1.5 No or incomplete drug treatment in spite of existing indication	Levetiracetam	The patient admitted with subdural haemorrhage was not being administered prophylactic antiseizure medication. The pharmacist recommended 1 g q12h of levetiracetam therapy with a duration of 7 days.
C1.2 No indication for drug	Cefazoline	The patient admitted for postoperative thyroidectomy was being administered antibacterial prophylaxis. The pharmacist recommended stopping the cefazoline therapy because clean procedures require no antibacterial prophylaxis.
C1.3 Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements	Clarithromycin	The patient was being administered clarithromycin and phenytoin therapy concomitantly. The pharmacist recommended replacing clarithromycin with azithromycin, which does not interact with phenytoin.
C1.4 Inappropriate duplication of therapeutic group or active ingredient	Furosemide	The patient admitted with decompensated heart failure was being administered intravenous and oral furosemide therapy concomitantly. The pharmacist recommended stopping oral furosemide therapy.
C1.1 Inappropriate drug according to guidelines/formulary	Dexamethasone	The patient admitted with a brain tumour was being administered dexamethasone therapy in an attempt to reduce the cerebral oedema. The pharmacist recommended stopping the dexamethasone therapy, since it was of no use in this case.
C1.6 Too many different drugs/active ingredients prescribed for indication	Tramadol	The patient was being administered fentanyl and tramadol therapy concomitantly as part of an

		analgosedation therapy. The pharmacist recommended stopping the tramadol therapy.
Other		
C9.2 Other cause	Normal saline	The patient was being administered normal saline despite that serum sodium level of the patient was 161 mmol/L. The pharmacist recommended replacing normal saline with 1/2 normal saline therapy.
C9.3 No obvious cause	Rivaroxaban	The patient was being administered rivaroxaban therapy. The pharmacist recommended the drug be withheld for 24 hours before the surgery.
C9.1 No or inappropriate outcome monitoring	Valproic acid	The patient was being administered valproic acid and meropenem therapy concomitantly; however, monitoring of the valproic acid level was not being performed. The pharmacist recommended that therapeutic drug monitoring of the valproic acid be performed.
Treatment duration		
C4.2 Duration of treatment too long	Hydrocortisone	The patient was being administered 50 mg q6h hydrocortisone therapy because of septic shock; however, the duration of therapy was beyond 7 days. The pharmacist recommended the hydrocortisone therapy be stopped with a taper.
Patient transfer related		
C8.1 Medication reconciliation problem	Valsartan-hydrochlorothiazide	For the patient being hypertensive, the pharmacist recommended his/her home antihypertensive medication to be administered.
Drug form		
C2.1 Inappropriate drug form/formulation (for this patient)	Levodopa-benserazide	Being fed via a nasogastric tube, the patient would be prescribed levodopa-benserazide capsules. The pharmacist recommended replacing capsule form with tablet form, as capsules should not be opened while tablets could be crushed.
Drug use process		
C6.1 Inappropriate timing of administration or dosing intervals by a health professional	Pyridostigmine	The patient with diarrhoea was administered pyridostigmine and continuous feeding. The pharmacist recommended replacing continuous feeding with bolus feeding and administering pyridostigmine with bolus feeding.
C6.6 Drug administered via wrong route by a health professional	Tamsulosin	For the patient who was unable to take the tamsulosin capsule orally, it was administered by opening the capsule. The pharmacist recommended replacing tamsulosin with doxazosin which could be crushed and administered via a nasogastric tube.