ORIGINAL ARTICLE
DOI: 10.4274/tjps.galenos.2023.47105

CLINICAL PHARMACIST-LED MEDICATION REVIEW IN HOSPITALIZED CONFIRMED OR PROBABLE PATIENTS WITH COVID-19 DURING THE FIRST WAVE OF COVID-19 PANDEMIC

Short Title: Clinical pharmacy in the COVID-19 pandemic

Duygu Under[1], Cüneyd Enver[1], Muhammed Yasir Demirci[1], Yunus Emre Ayhan[1], Betül Özgan[1], Enes Emir Ilerler[1], Betul Okuyan[1], Buket Ertürk Şengel[2], Derya Kocakaya[3], Uluhan Sili[2], Elif Tukenmez Tigen[2], Sait Karakurt[3], Volkan Korten[2], Mesut Sancar[11]Clinical Pharmacy Department, Faculty of Pharmacy, Marmara University, Istanbul,
[2]Department of Infectious Diseases and Clinical Microbiology, School of Medicine Marmara University, Istanbul, Turkey.
[3]Department of Pulmonary Medicine, School of Medicine, Marmara University, Istanbul, Turkey.

Corresponding Author Information
Mesut Sancar
https://orcid.org/0000-0002-7445-3235
sancarmesut@yahoo.com
20.03.2023
06.06.2023
28.08.2023

Abstract
Objectives: Drug-related problems result in serious problems among hospitalized patients and high rate of morbidity and mortality, and increased healthcare costs. It is aimed to identify drug-related problems by clinical pharmacist-led medication review in hospitalized probable patients with COVID-19 during the first wave of COVID-19 pandemic.
Methods: This retrospective cross-sectional study was conducted at COVID-19 inpatient services of a tertiary university hospital in Turkey for 3 months (between March 2020 and June 2020) and included hospitalized confirmed or probable COVID-19 patients. World Health Organization (WHO) and Turkish Ministry of Health Guidelines case definitions were used to define confirmed and probable COVID-19 patients. Six clinical pharmacy residents provided medication review service during their education and training. Drug-related problems were classified based on Pharmaceutical Care Network Europe (PCNE) V9.00. The physician's acceptance rate of clinical pharmacists' recommendations was assessed.
Results: Among 202 hospitalized patients with probable or confirmed COVID-19, 132 patients (65.3%) had at least one drug-related problem. Two hundred sixty-four drug-related problems were identified. Drug selection (85.6%) and dose selection (9.2%) were the most common causes of these problems. Among the 80 clinical pharmacist interventions, 48.8% were accepted by the physicians.
Conclusion: Clinical Pharmacists have identified a significant number of DRPs during the COVID-19 pandemic, particularly those related to drug interactions and drug safety such as ADRs. This study highlights the importance of detecting and responding to DRPs in the COVID-19 pandemic.
Keywords: COVID-19, medication review, clinical pharmacist, drug-related problem, PCNE

INTRODUCTION

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

Several clinical trials have continued to evaluate the efficacy and safety of specific drugs in COVID-19 patients.[4] Repurposed drugs for COVID-19 are given to treat patients at home, leading to adverse drug events or drug-drug interactions.[5] During the COVID-19 pandemic, clinical pharmacists continue to provide services such as medication review, medication reconciliation, patient education and counseling, and therapeutic drug monitoring in hospitalized patients with COVID-19.[6-7]

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

Clinical pharmacy postgraduate education program (M.Sc. and Ph.D.) has been maintained in Turkey since 1991. Clinical pharmacist specialist education and training program has been started by the Turkish Ministry of Health in 2018. However, clinical pharmacy services are not included as essential requirements at the hospitals in Turkey yet.

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

METHODS

This retrospective cross-sectional study was conducted in COVID-19 inpatient services, including infectious diseases, pulmonary medicine, and internal medicine wards of a tertiary university hospital in Istanbul, Turkey, for three months (between March 2020 and June 2020). All patients (>18 years old) hospitalized for confirmed or probable COVID-19, stayed at the hospital more than 24 hours, used at least one drug during their hospitalization, and received the clinical pharmacist-led medication review service during their hospitalization were included. The patients transferred to the intensive care unit during the first 24 hours of their hospitalization were excluded from the study. Our study was conducted in 4 clinics; the total number of beds is 60 and a total of 8 doctors, 2 doctors in each clinic, worked. 3 clinical pharmacists worked in the clinics alternately, while 3 clinical pharmacists supported the study remotely.

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

Patient's demographic (including age and sex), clinical (including comorbidities), and laboratory data [including complete blood count, LDH, creatinine, coagulation tests, procalcitonin, CRP], the result of real-time reverse transcription-polymerase chain reaction (real-time RT-PCR) test from nasopharyngeal specimens were anonymously recorded to the patient follow and evaluation form. Biochemical data were recorded on the first day of hospitalization of the patient. In all patients, Charlson Comorbidity Index was calculated.[12]

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

Clinical pharmacist residents assessed all the medication orders of the hospitalized patients with confirmed and probable COVID-19. The potential drug-drug interactions were evaluated using Lexicomp® Drug Interactions (Wolters Kluwer Health Inc., 2020), Micromedex® Drug Information, and Drug Interactions (Truven Health Analytics Inc., 2020). International guidelines in UpToDate Drug Information and Micromedex Drug Information and national guideline of COVID-19 for adult patients published by

the Turkish Ministry of Health were used to evaluate the appropriateness of drugs. Drug-related problems were classified using Pharmaceutical Care Network Europe (PCNE) V9.00 – Turkish Version.[15] PCNE, one of the most widely used classification systems, was used to classify DRP in hospital practice.[9,16] PCNE has been translated into various languages in countries where the clinical pharmacy is practiced[15,17] and consists of five parts: problem, cause, intervention, intervention acceptance, and status. The "status of DRP" could not be evaluated in PCNE because the study was retrospective. The type and reason of all drug-related problems, the rate of clinical pharmacists' recommendations, and the physician's acceptance rate of clinical pharmacists' recommendations were assessed.

Statistical Analysis

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

Ethics Approval

The study protocol was approved by the local Clinical Research Ethical Committee of the XXX University School of Medicine (The approval number: 09.2020.668).

RESULTS

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

The median of DRPs/patients was 1.3. In Table 3, the incidence of DRPs was "treatment effectiveness" (55 of 264 DRPs; 20.8 %) followed by "treatment safety" (140 of 264 DRPs; 53.0%). Within the "treatment effectiveness" category, the "untreated symptoms or indication" was the dominant category (46 of 140; 32.9 %). A total of 270 DRP causes were identified (Table 4). "Drug selection" category was the primary cause of DRPs (231 of 270; 85.6 %) followed by "drug dose" (25 of 270; 9.3 %). Among drug selection problems, the most common DRPs were "inappropriate combination of drugs or drugs and herbal medication", "no indication for drug" and "no drug treatment despite existing indication" (108 of 231, 46.8%; 54 of 231, 23.4% and 47 of 231, 20.3%; respectively). The combination of azithromycin-hydroxychloroquine constitutes 52.8% of drug-drug interactions. In 112 planned interventions, 91.1% were at the prescriber level. According to the PCNE classification, 80 (71.4) interventions were proposed to the prescriber. Thirty-nine (48.8%) interventions were accepted, and the acceptance status of 33 (41.3%) interventions was unknown. Only 8 (10.0%) interventions were rejected.

Discussion

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

In our study involving COVID-19 patients, the incidence of DRP was found to be similar to another study performed on COVID-19 patients (1.4 DRP/patient).[18] Similar rate DRP has been detected in studies involving COVID-19 patients.[5,19,20] DRP rates were found to be higher in studies conducted before the COVID-19 pandemic.[21] The reason for our low DRP rates may be that the study was planned retrospectively in a period under pandemic conditions. Problems with drug safety were identified, including most DRPs, potential drug interactions, ADRs, and high doses. Similar to other studies, the most frequently detected DRP was "treatment safety" (53%) and then "treatment effectiveness" (20%).[19,20] Drug interactions accounted for approximately 40% of the total causes of DRP; the reason for this high rate compared to other studies may be the

frequent use of hydroxychloroquine and azithromycin, which are drugs used in the COVID-19 pandemic. The risk of QT prolongation is increased with the combined use of hydroxychloroquine and azithromycin; most clinical pharmacists' recommendations have been this interaction. Proton pump inhibitors (PPIs) are often overprescribed, and overprescribing has continued in the COVID-19 pandemic. Clinical pharmacists advised physicians to optimize PPI use. Long-term use of PPIs has been associated with adverse events such as pneumonia. Analysis of clinical pharmacist interventions in COVID-19 units found that PPI was overprescribed in a similar study.[5] In our study, similar rates of "No drug indication" and "No drug treatment despite the current indication" were found among DRP causes, and it is thought that it may be due to the difficulty of medication reconciliation in pandemic conditions.

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

Half of the interventions proposed due to DRPs were accepted in our study. In different studies conducted before the pandemic, the acceptance rate of the interventions was found to be higher.[21,22] During the COVID-19 pandemic, clinical pharmacists continued to provide services such as medication reconciliation, medication review, therapeutic drug monitoring, patient education, and counseling for patients hospitalized with COVID-19 over the phone or by working remotely.[7,23] The limited performance of clinical pharmacy services due to situations such as the inability to take a medication history from the patient, the patients being in isolation conditions, the clinical pharmacist's inability to visit the patient and remote work, and the daily change of the physicians who follow the patients and the pharmacists who make suggestions may have caused the acceptance rates to be low. Due to the first wave of the pandemic, the strict implementation of protective measures, and the remote working conditions, acceptance rates could not be followed very well in resolving drug-related problems. In addition, in a published article, it was stated that the acceptance rate of the recommendations made by pharmacists during the pandemic was lower than before the pandemic due to less effective communication and the need for more intensive follow-up to be accepted.[7]

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

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

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

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

Conclusion

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

Acknowledgment

None

Funding

None

Conflicts of interest

None

References

1. Zhu N, Zhang D, Wang W, *et al*.A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020;382:727-733.
2. World Health Organization. *COVID-19* Weekly Epidemiological Update. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-january-2022 (accesed 25 Jan 2022).
3. World Health Organization. Coronavirus disease 2019 (COVID-19): Case Definitions, Updated in Public health surveillance for COVID-19. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2 (accessed 10 Aug 2020).
4. Li L, Li R, Wu Z, Yang X, Zhao M, Liu J, Chen D. Therapeutic strategies for critically ill patients with COVID-19. Ann Intensive Care. 2020;10:45.
5. Perez M, Masse M, Deldicque A, Beuscart JB, De Groote P, Desbordes J, Fry S, Musy E, Odou P, Puisieux F, Lambert M, Scherpereel A, Décaudin B. Analysis of clinical pharmacist interventions in the COVID-19 units of a French university hospital. Eur J Hosp Pharm. 2022;29:e30-e35.
6. Paudyal V, Cadogan C, Fialová D, Henman MC, Hazen A, Okuyan B, Lutters M, Stewart D. Provision of clinical pharmacy services during the COVID-19 pandemic: Experiences of pharmacists from 16 European countries. Res Social Adm Pharm. 2021;17:1507-1517.
7. Surapat B, Sungkanuparph S, Kirdlarp S, Lekpittaya N, Chunnguleum K. Role of clinical pharmacists in telemonitoring for patients with Coronavirus Disease 2019 (COVID-19). J Clin Pharm Ther. 2021;46:236-239.
8. Griese-Mammen N, Hersberger KE, Messerli M, Leikola S, Horvat N, van Mil JWF, Kos M. PCNE definition of medication review: reaching agreement. Int J Clin Pharm. 2018;40:1199-1208.
9. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. *Br J Clin Pharmacol* 2012;74:573-80.
10. Kefale B, Degu A, Tegegne GT. Medication-related problems and adverse drug reactions in Ethiopia: A systematic review. *Pharmacol Res Perspect* 2020;8:00641.
11. Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. Drug-related problems: their structure and function. DICP. 1990;24:1093-7.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
13. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report, 61. Geneva. 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200321-sitrep-61-covid-19.pdf (accessed 10 Aug 2020).
14. T.C. Sağlık Bakanlığı COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi, Bilim Kurulu Çalışması. Genel Bilgiler, Epidemiyoloji ve Tanı. 2020. https://covid19.saglik.gov.tr/TR-66337/genel-bilgiler-epidemiyoloji-ve-tani.html (accesed 10 Aug 2020).
15. Pharmaceutical Care Network Europe (PCNE). The definition of drug-related problems. 2020. https://www.pcne.org/upload/files/417_PCNE_classification_V9-1_final.pdf (accessed 10 Aug 2020).
16. Saldanha V, Randall Martins R, Lima SIVC, Batista de Araujo I, Gouveia Oliveira A. Incidence, types and acceptability of pharmaceutical interventions about drug related problems in a general hospital: an open prospective cohort. BMJ Open. 2020;10:e035848.
17. Schindler E, Richling I, Rose O. Pharmaceutical Care Network Europe (PCNE) drug-related problem classification version 9.00: German translation and validation. *Int J Clin Pharm* 2021;43:726-730.
18. Barceló-Vidal J, Carballo N, De Antonio-Cuscó M, Fernández-Sala X, Echeverría-Esnal D, Acín P, López-Mula C, Comella-Anaya L, González-Colominas E, Luque S, Ferrández O. Potential drug related problems in the time of COVID-19. *Eur J Hosp Pharm* 2021;28:105-106.
19. Chappe M, Corvaisier M, Brangier A, Annweiler C, Spiesser-Robelet L. Impact of the COVID-19 pandemic on drug-related problems and pharmacist interventions in geriatric acute care units. Ann Pharm Fr. 2022 Sep;80(5):669-677.
20. Gourieux B, Reisz F, Belmas AS, Danion F, Fourtage M, Nai T, Reiter-Schatz A, Ruch Y, Walther J, Nivoix Y, Michel B. Prescribing practices of lopinavir/ritonavir, hydroxychloroquine and azithromycin during the COVID-19 epidemic crisis and pharmaceutical interventions in a French teaching hospital. Eur J Hosp Pharm. 2021 Sep;28(5):242-247.
21. 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.

22. Li Q, Qu HJ, Lv D, *et al*. Drug-related problems among hospitalized patients with COPD in mainland *China. Int J Clin Pharm* 2019;41:1507-1515.
23. Li H, Zheng S, Liu F, Liu W, Zhao R. Fighting against COVID-19: Innovative strategies for clinical pharmacists. Res Social Adm Pharm. 2021;17:1813-1818.

Table 1. Patients' characteristics (N=202)

Characteristics	**Total patients (n=202) n (%)**	**Patients with DRP (n=132) n (%)**	**Patients without DRP (n=70) n (%)**	***p***
Sex				
Male	97 (48.0)	62 (47.0)	35 (50.0)	NS
Female	105 (52.0)	70 (53.0)	35 (50.0)	
Age				
Median	59.0 (18.3)	58.8 (1.6)	60.1 (2.1)	NS
Older patients (≥65 years old)	78 (38.6)	51 (38.6)	27 (38.6)	NS
Charlson Comorbidity Index				
Median (IQR)	2.0 (1.0-4.0)	3.0 (1.0-4.0)	2.0 (1.0-4.0)	NS
Total number of medications				
Median (IQR)	6.0 (4.0-8.0)	6.0 (4.0-8.8)	5.0 (3.0-7.0)	< 0.01
The classification based on total number of medications				
<5	76 (37.6)	45 (34.1)	31 (44.3)	NS
≥5	126 (62.4)	87 (65.9)	39 (55.7)	
The duration of hospitalization (day)				
Median (IQR)	7.0 (4.0-11.0)	7.0 (4.0-11.0)	7.0 (5.0-14.5)	NS
Result of SARS-CoV-2 RT-PCR test				
Positive	112 (55.4)	72 (54.6)	40 (57.2)	NS
Negative	83 (41.1)	54(40.9)	29 (41.4)	
Unknown/missing data	7 (3.5)	6(4.5)	1 (1.4)	
The number patient who received COVID-19 treatment				

Yes	182 (90.1)	118 (89.4)	64 (91.4)	NS
No	20 (9.9)	14 (10.6)	6 (8.6)	
The most common used medication in management of COVID-19				
Hydroxychloroquine	176 (87.1)	115 (87.1)	60 (85.7)	NS
Enoxaparin	142 (70.3)	93 (70.5)	49 (70.0)	NS
Azithromycin	57 (28.2)	42 (31.8)	15 (21.4)	NS
Favipiravir	53 (26.2)	30 (22.7)	23 (32.9)	NS
Oseltamivir	7 (3.5)	4 (3.0)	3 (4.3)	NS
Tocilizumab	5 (2.5)	1 (0.8)	4 (5.7)	NS

IQR: interquartile range; DRP: medication related problem; NS: no significant; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2, RT-PCR: reverse transcriptase polymerase chain reaction.

Table 2. Patients' biochemical parameters related with COVID-19 (N=202)

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

ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; CRP: C-reactive protein; IQR: interquartile range; LDH: lactate dehydrogenase; DRP: medication related problem; NS: no significant; PT: prothrombin time

Table 3. Medication related problems (DRP) based on Pharmaceutical Care Network Europe (PCNE) V9.00 (n=132)

	Detailed Classification (Code V9.0)	**n (%)**
Type of DRP (Code V9.0) (n=264)		
Treatment effectiveness (P1)	Untreated symptoms or indication (P1.3)	46 (17.4)
	Effect of drug treatment not optimal (P1.2)	9 (3.4)
Treatment safety (P2)	Adverse drug event (possibly) occurring (P2.1)	140 (53.0)
Others (P3)	Unnecessary drug-treatment (P3.2)	60 (22.7)

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

*More than one cause was determined for each DRP