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ORIGINAL RESEARCH

Antimicrobial stewardship practices in the intensive care unit: a pre–post interventional study

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ABSTRACT

Objective: This study aims to assess the frequency of drug-related problems (DRPs) related to antimicrobial drugs in the ICU and to examine changes in the use of antibiotics in the 'Reserve' group of the World Health Organization (WHO) AWaRe classification during the antimicrobial stewardship (AMS) team intervention, including the clinical pharmacist.

Methods: In this single-center intervention study, the pre-intervention period between November 2021 and August 2022 and the post-intervention period between November 2022 and August 2023 were evaluated. In the post-intervention period, a clinical pharmacist was also included in the AMS team. Post-intervention medication-related problems (DRPs) were categorized using only the "problem" and "cause" domains of the Pharmaceutical Care Network Europe (PCNE) V9.1 classification system. Additionally, recommendations and their acceptance rates were recorded. The antibiotic use density of the 'Reserve' group, defined in the WHO AWaRe classification, was evaluated in terms of days of therapy (DOT) per 1000 patient-days.

Results: After the intervention, 175 DRPs were detected in 67.1% of 173 patients; 70% were related to antimicrobial drugs. The 90.1% of the interventions suggested by the clinical pharmacist were evaluated and accepted by infectious diseases and intensive care specialists. The total use of "Reserve" group antibiotics decreased, but not significantly; significant decreases were observed for some agents such as linezolid and daptomycin.

Conclusion: Multidisciplinary antimicrobial stewardship practices involving the clinical pharmacist can contribute to the prevention of antimicrobial resistance development by facilitating the detection and solution of DRPs, especially by reducing the use of 'Reserve' group antimicrobials.

Keywords: antimicrobial resistance, antimicrobial stewardship, intensive care unit

Introduction

Antimicrobial resistance (AMR) poses a substantial threat to global public health and progress. In 2019, bacterial antimicrobial resistance (AMR) directly caused 1.27 million deaths and indirectly caused 4.95 million deaths over the world (1). The 2015 OECD data indicates that Turkey has the highest resistance rate among OECD countries at 38.8%, despite a 15-year antibiotic limitation program in hospitals (2).

Intensive care units (ICUs) use a high number of broad-spectrum antibiotics, emphasizing the need for conservation efforts (3). Using antibiotics

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inappropriately in ICUs can result in drug-resistant organisms emerging, posing a serious threat to patient health (4). In addition, subtherapeutic drug concentrations may promote the growth of resistant microorganisms in critically ill patients (5).

Antimicrobial stewardship (AMS) has become an important strategy to tackle antimicrobial resistance. In 2017, the WHO classified antibiotics into three categories: Access, Watch, and Reserve (WHO's AWaRe classification) (6). In the Reserve group, antibiotics should be regarded as a "last resort," available for prescription solely to very specific patients and circumstances where all other options have proven ineffective or inappropriate. The WHO Model List of Essential Medicines includes seven antibiotics from the Reserve group (7). In hospitals, these are commonly used, and so have been targeted for AMS interventions (6,8,9). Integrating clinical pharmacy services, including AMS practices, in intensive care settings is crucial to optimizing antimicrobial use, improving patient outcomes, and combating antimicrobial resistance. In ICUs, it is vital that clinical pharmacists, infectious disease physicians, and intensivists to drive successful AMS initiatives (10-15).

Although various national strategy documents (2,16) have been published in Turkey to combat antimicrobial resistance, the implementation of the AMS program is still not mandatory at the national level. Therefore, AMS implementations largely depend on the individual initiative and institutional motivation of healthcare institutions. The lack of a standard legislative infrastructure indicates a significant policy gap in terms of the sustainability and widespread impact of these programs. An effective AMS approach requires not only technical implementations but also strong health policy support (17). In this context, making AMS programs, which are carried out by multidisciplinary teams including clinical pharmacists, mandatory at the institutional level by supporting them with legal regulations will contribute to Turkey creating a stronger and more sustainable roadmap in the fight against antimicrobial resistance.

The objective of this study is to assess the effects of AMS team interventions, including those by clinical pharmacist, on the subsequent outcomes: (i) the prevalence of antimicrobial drug-related problems (DRPs) by using the Pharmaceutical Care Network Europe (PCNE) V9.1 classification. (ii) the change in the frequency of antibiotic usage via the "Reserve" group of the WHO's AWaRe classification.

Materials and methods

Study design and patients

This single-center intervention study was carried out in two phases: the pre-intervention phase from November 2021 to August 2022, and the post-intervention phase from November 2022 to August 2023, at the adult medical and surgical ICU of Baskent University Ankara Hospital, a tertiary academic institution with a capacity of 500 beds. The ICU is a closed unit with 18 beds and is a mixed unit that accepts critically ill patients from internal medicine and surgical branches. This is the only ICU in the hospital and all adult patients requiring intensive care (including internal medicine, surgical, neurological and oncological patients) are admitted to this unit. The unit has the infrastructure to provide advanced life support such as mechanical ventilation, renal replacement therapy and continuous hemodynamic monitoring.

In this study, all patients admitted to the ICU and receiving antimicrobial drugs were included. The Declaration of Helsinki was followed during the conduct of this study.

Description of AMS team

The AMS team, which consisted of infectious disease physicians, intensivists, and a clinical pharmacist, followed patients in the 18-bed ICU. In November 2022, a clinical pharmacist joined the AMS team of intensivists and infectious disease physicians. The November-August 2021 data and the November-August 2022 data, which included a multidisciplinary team, were evaluated.

In the pre-AMS period, antimicrobial treatment processes were carried out only by infectious diseases and intensive care specialists. During this period, there was no clinical pharmacist, and DRPs were not systematically evaluated. Treatment decisions were generally made individually based on clinical observation, culture results, and physician experience. During the AMS period, with the clinical pharmacist on the team, each patient's antimicrobial medication was checked on a regular basis, DRPs were found using the PCNE V9.1 classification, and ideas for solutions were offered. During this period, AMS practices acquired a multidisciplinary structure and antimicrobial use processes became more structured.

Inclusion criteria

Adult patients hospitalized in the intensive care unit for ≥7 days and treated with antimicrobial therapy were included in this study. In clinical practice, all intensive care patients are evaluated by the AMS team; however, in this study, only patients who stayed in the ICU for ≥7 days were included in the analysis in order to systematically observe DRPs and to make meaningful comparisons between the two periods.

Drug-related problems and PCNE

Drug-related problems (DRPs) are occurrences or circumstances that hinder the achievement of intended therapeutic outcomes, as defined by Pharmaceutical Care Network Europe (PCNE). The PCNE is a mechanism employed to categorise Drug-Related Problems (DRP). The report comprises five primary sections: issues, causes, proposed interventions, acceptance of interventions, and DRP status (16). In the post-intervention period, DRPs were classified using only the "problem" and "cause" domains of the PCNE V9.1 classification system. The recommendations made for these problems and the acceptance rates of the recommendations were also recorded and analyzed.

Clinical pharmacist intervention

During the study period, a clinical pharmacist participated in rounds with physicians. Pharmacist conducted the primary review, screened cases for appropriateness, determined DRPs, and recommended therapy. The clinical pharmacist's purpose was to assist physicians in identifying, preventing, or resolving issues linked to medications, including side effects, misuse, needless usage, interactions, missing or overdosed medications, and adverse events. The clinical pharmacist made therapeutic recommendations regarding antimicrobial and non-antimicrobial drug treatments; these recommendations were discussed with the infectious diseases specialist and the intensive care specialist, the final decision was made and implemented.

Data collection and measurement of antimicrobial use

The collected data encompassed clinical and demographic information, in addition to antibiotic usage, quantified in days of therapy (DOT). To determine the amount of "Reserve" group antibiotic (7) used, days of therapy were calculated per 1000 patient days (PDs).

Statistical analysis

The study's statistical analysis showed quantitative data using mean, standard deviation, median, maximum and lowest values, and percentages. Qualitative data were shown as counts and percentages. The Shapiro-Wilk test was employed to evaluate the normality of the data. The Chi-square test with Fisher's exact correction was used to look at differences between groups for categorical data, and the t-test was used for continuous variables. A P-value of less than 0.05 was used to show that the results were statistically significant. The analysis was done with IBM SPSS version 25.0 software.

Results

The pre-IP included 168 patients, while the post-IP included 173 patients. The quantity of female patients increased in the post-IP period (47.0% vs 58.1%, p=0.040). In both periods, most patients had 3-5 comorbidities (55.9% vs 50.8%, p=0.557). Apache II score was higher post-IP (17.3±6.2 vs 19.2±7.7, p=0.015) (Table 1).

A total of 175 DRPs were identified in 116 patients, constituting 67.1%, by clinical pharmacy (CP) in the post-intervention period (post-IP). The predominant class of medication in DRPs was antibacterial agents, accounting for 70.0%. The predominant antimicrobial-associated drug-related problems were dose-related (53.1%) (Table 2). Ninety percent of the measures proposed by the clinical pharmacist were assessed and approved by specialists in infectious illnesses and intensive care.

The total number of "Reserve" group antibiotic DOTs per 1000 PDs decreased from 43.7 in the pre-IP to 28.5 in the post-IP, but not significantly (p> 0.340). When the pre-interventional and interventional periods were compared, the DOTs of polymyxin B, linezolid, daptomycin, and tigecycline were 0.0 vs 5.9 (p=0.048), 14.4 vs 4.6 (p=0.012), 3.8 vs 0.0 (p=0.042), 0.0 vs 5.9 (p=0.003) days, respectively (Table 3).

The mean duration of hospital stay was 12.4 ± 5.0 days prior to the intervention and 12.9 ± 3.9 days following the intervention (p = 0.988). The thirty-day all-cause mortality rates were determined to be 28.0% during the pre-intervention period and 27.7% in the post-intervention period (p = 0.962).

Discussion

This study shows that the integration of clinical pharmacists into the AMS program in the intensive care unit enables more effective identification of DRPs related to antimicrobial drugs. The vast majority of these interventions are accepted by the AMS team and incorporated into the treatment processes. The high rate of DRPs in the post-intervention period, 31.4%, reveals how common these problems can be in clinical practice and supports the necessity of an active pharmaceutical perspective in AMS practices.

In particular, the fact that 70% of the detected DRPs are related to antimicrobial drugs shows that this drug group has both a high frequency of use and a delicate balance between incorrect/correct use in intensive care. Although the majority of DRPs were for antimicrobial drugs, the AMS team also identified and intervened in problems with non-antimicrobial drugs. Approximately 30% of DRPs were for other drug groups and included problems such as dosage errors, drug interactions, and repeat treatments. This also demonstrates the contribution of the clinical pharmacist to the overall optimization of pharmacotherapy in the ICU. This makes it even more important for the clinical pharmacist to recognize problems such as dosing errors in antibiotic use,

Table 1. Patient characteristics.

Parameters	Pre-IP (n= 168)	Post-IP (n= 173)	p-value
Age, mean ± sd	75.3 ± 14.8	74.6 ± 13.1	0.162
Female sex, n (%)	79 (47.0)	100 (58.1)	0.040*
Number of comorbidities, n (%)			
0	4 (2.4)	4 (2.3)	0.557
1-2	51 (30.3)	61 (35.3)	
3-5	94 (55.9)	88 (50.8)	
>5	19 (11.4)	20 (11.6)	
Apache II score, mean ± sd	17.3 ± 6.2	19.2 ± 7.7	0.015*

* p value < 0.05.

inappropriate antibiotic selection, or unnecessary combination therapies. Similarly, it has been reported in the literature that DRP rates in intensive care patients can be reduced with clinical pharmacist interventions and that the clinical outcomes of the patients are also improved (11,13). Studies conducted by clinical pharmacists in the intensive care unit in Türkiye and aimed at identifying drug-related problems also

Table 2. Aetiologies of DRPs according per PCNE.

Cause of the problem	PCNE Code	Number and Frequency (%)
Drug selection	C1	48 (37.5)
Inappropriate drug according to guidelines/formulary		
No indication for drug		
Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements		
Inappropriate duplication of therapeutic group or active ingredient		
No or incomplete drug treatment in spite of existing indication		
Too many different drugs/active ingredients prescribed for indication		
Dose selection	C3	68 (53.1)
Drug dose too low		
Drug dose of a single active ingredient too high		
Dosage regimen not frequent enough		
Dosage regimen too frequent		
Dose timing instructions wrong, unclear or missing		
Drug use process	C6	5 (3.9)
Inappropriate timing of administration or dosing intervals by a health professional		
Drug under-administered by a health professional		
Drug over-administered by a health professional		
Drug not administered at all by a health professional		
Wrong drug administered by a health professional		
Drug administered via wrong route by a health professional		
Other	C9	7 (5.5)
No or inappropriate outcome monitoring (incl. TDM)		
Other cause; specify		
No obvious cause		

Table 3. Compared to the use of DOT of "reserve" group antimicrobials.

Antimicrobial drugs	Pre-IP (n= 168)	Post-IP (n= 173)	p-value
Ceftazidime avibactam	5.8	2.9	0.445
Colistin	14.4	7.5	0.225
Polymyxin B	0.0	5.9	0.048*
Fosfomycin	5.3	1.7	0.215
Linezolid	14.4	4.6	0.012*
Daptomycin	3.8	0.0	0.042*
Tigecycline	0.0	5.9	0.003*
Total	43.7	28.5	0.340

* p value < 0.05.

show consistent results. For example, Albayrak et al. reported that DRP was detected in 71.5% of intensive care patients and that most of these problems were due to dosing and drug selection errors; it was shown that these problems were resolved by 90.8% after clinical pharmacist interventions (18). Similarly, in the study by Ayhan et al., a decrease in drug costs and an increase in patient safety were achieved with the reduction of DRPs (19).

The clinical pharmacist's proposed therapies were accepted at a rate of 90.1%. This rate can be considered as a successful example of multidisciplinary teamwork. In the ICU, rapid and effective decisions regarding treatment are required, especially due to time pressure and complex patient profiles. The participation of the clinical pharmacist in patient visits allows them to contribute to the treatment process directly; this both increases the applicability of the recommendations and provides support to the physician. These findings are parallel to the study conducted by Hashimoto et al.(10) it was reported that more than 80% of the recommendations of clinical pharmacists in the intensive care unit were accepted and guided the treatment.

An important indicator of antibiotic use monitored in the study was the change in the use of the "Reserve" group antibiotics in the WHO AWaRe classification. Although the total use rate decreased after the intervention (from 43.7 to 28.5 DOT/1000 patient-days), this difference was not found to be statistically significant. However, significant decreases were detected for some agents (e.g. linezolid, daptomycin). This suggests that the AMS team focused on using high-risk and broad-spectrum agents more selectively, considering not only the total antibiotic use but also the rationality of antimicrobial therapy. Similarly, in the study conducted by Özger et al., it was stated that gram-positive spectrum antibiotics such as linezolid and daptomycin were frequently used empirically, and 83% inappropriate prescribing was detected (20). This situation emphasizes the necessity of using reserved group antibiotics carefully and in accordance with the guidelines. WHO recommends that these drugs be used only in serious, resistant infections and when alternatives have failed (7). In this context, it can be said that the AMS team brought their treatment choices closer to these principles.

In contrast, a significant increase in the use of polymyxin B was observed in the post-intervention period. This increase may be related to the lower nephrotoxicity of polymyxin B compared to colistin, which is frequently used in the treatment of multidrug-resistant gram-negative infections. In clinical practice, polymyxin B has been preferred over colistin because it offers a safer profile (21,22) despite having similar antimicrobial activity in patients with renal dysfunction. Therefore, it can be said that the increase in the use of polymyxin B reflects the rational agent choices made by the AMS team based on patient characteristics and drug safety profiles.

The study found no significant difference in mortality rates (28% vs. 27.7%) and length of hospital stay. However, since the aim of the study was to improve antimicrobial treatment processes rather than directly change these parameters, no significant difference in short-term clinical outcomes is expected. Long-term effects of AMS implementations—such as changes in resistance rates, prevention of adverse events, and reduction of healthcare system costs—usually require longer follow-up periods (6,9). A similar result was also observed in a study focusing on colistin use by Albayrak et al.; while the appropriate use rate increased thanks to clinical pharmacist interventions, the nephrotoxicity rate decreased significantly, but no significant difference was found in mortality rates (23). A majority of the interventions evaluated in the study were optimizing interventions, such as dose adjustments or de-escalation, which have a positive effect on the quality of care without directly impacting mortality.

An important aspect of this study is that it is one of the few studies conducted in a university hospital in Turkey that evaluates the integration of clinical pharmacists

into the AMS team. However, some limitations should be taken into account. The study is single-center and the sample size is limited; therefore, its generalizability is limited. In addition, secondary outcomes such as cost-effectiveness of the interventions, changes in resistance profiles, and prevention of adverse drug reactions were not evaluated. Also, the inclusion of only patients with ≥7 days in the ICU may be an important limitation, considering that patients with shorter hospitalizations may also develop DRP. However, this criterion was determined for systematic analysis purposes, as shorter hospitalizations do not provide sufficient observation time for the development of DRP and follow-up of interventions. Another limitation is detailed clinical data such as comorbidities, reasons for hospitalization, infection indications and renal function of the patients included in the study were not recorded systematically due to limitations in the retrospective data collection process. Therefore, they could not be included in the analysis. This was considered an important limitation of the study and detailed clinical characteristics are planned to be included in future studies. In the study, only the intensity of use of the "Reserve" group antibiotics was evaluated, and comparative data for all antibiotic classes were not collected. In addition, since the dosage and application errors were not recorded in detail, detailed analysis of these DRP types could not be presented. These situations are among the important limitations of the study. These areas provide important ground for future studies.

In conclusion, the participation of clinical pharmacists in the AMS team contributed to more effective identification of drug-related problems in the intensive care unit and optimisation of treatment processes. A trend towards a decrease in the use of "reserve" group antibiotics and total DOT values was observed, but these changes were not statistically significant. Since there is no data on the development of antimicrobial resistance in this study, no conclusions can be drawn on this issue. Future studies should evaluate patient-centred outcomes and their impact on resistance development.

Ethical approval

This study has been approved by the Baskent University Institutional Review Board (approval date: January 2, 2025, number: KA24/458). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: AP, BB; data collection: AP, TYY, FİY, HŞ, NS; analysis and interpretation of results: AP, TYY, FİY, HŞ, NS, ÖKA, PZ, BB; draft manuscript preparation: AP. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL RESEARCH

The effect of obesity on inflammatory response in intensive care patients with sepsis: CRP and procalcitonin analysis

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ABSTRACT

Objective: This study aimed to evaluate the independent effect of obesity on C-reactive protein (CRP) and procalcitonin levels in intensive care unit (ICU) patients with sepsis.

Methods: This retrospective, single-center observational study included adult patients admitted to the ICU with a diagnosis of sepsis or who developed sepsis during ICU follow-up between January and December 2025. Patients were classified as non-obese (BMI <30 kg/m²) or obese (BMI ≥30 kg/m²). CRP, procalcitonin, and Sequential Organ Failure Assessment (SOFA) scores were recorded at the time of sepsis diagnosis. Mann–Whitney U and chi-square tests were used for group comparisons; the independent effect of obesity was assessed by multivariable regression analysis.

Results: A total of 359 sepsis patients were included; 81 (22.6%) were obese. No significant differences were observed between groups in terms of age, SOFA score, or Charlson Comorbidity Index (CCI). Although CRP and procalcitonin levels showed a trend toward higher values in the obese group, no statistically significant difference was detected (p=0.135 and p=0.260, respectively). In multivariable analysis, obesity was not independently associated with CRP (expβ 1.16; 95% CI 0.86–1.56; p=0.321) or procalcitonin (expβ 1.49; 95% CI 0.88–2.51; p=0.136) levels. ICU mortality was similar between groups (63.0% vs. 68.3%; p=0.439).

Conclusion: No independent effect of obesity on CRP and procalcitonin levels was demonstrated at the time of sepsis diagnosis. Clinical context and concomitant metabolic conditions should be taken into account when interpreting inflammatory biomarkers in obese patients with sepsis.

Keywords: sepsis, obesity, C-reactive protein, procalcitonin, intensive care unit

Introduction

Sepsis remains one of the leading causes of mortality and morbidity in intensive care units (ICUs) worldwide. According to the Sepsis-3 consensus definition, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). The heterogeneity of the host response substantially influences both the clinical course of sepsis and the diagnostic and prognostic value of inflammatory biomarkers.

Obesity is a clinically important condition that can modulate the inflammatory response during sepsis through chronic low-grade inflammation, adipokine dysregulation, and alterations in immune function. The secretion of pro-inflammatory cytokines such as interleukin-6, tumour necrosis factor-alpha, and leptin by adipose tissue may lead to both quantitative and qualitative differences in the host response to infection in obese patients (2,3).

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C-reactive protein (CRP) and procalcitonin (PCT) are widely used inflammatory biomarkers for diagnosing and monitoring sepsis. CRP is an acute-phase protein synthesised in the liver in response to inflammation; its baseline levels may be elevated in the context of obesity-related chronic low-grade inflammation (4). PCT, in contrast, is a marker that rises markedly in bacterial infections but is suppressed in viral infections (5). Although adipose tissue has been shown to produce PCT and obesity-associated hyperprocalcitonaemia has been documented, the clinical relevance of this phenomenon in the setting of acute sepsis remains unclear (6,7).

The relationship between obesity and sepsis mortality has been debated within the framework of the "obesity paradox." At the same time, some studies have reported reduced mortality in obese patients; these findings remain inconsistent, particularly in cohorts comprising elderly and critically ill patients (8,9). Whether CRP and PCT responses at the time of sepsis diagnosis are independently altered in the presence of obesity represents a question of critical clinical importance, since standard biomarker threshold values have largely been established in non-obese populations and their direct extrapolation to obese patients rests on an assumption that warrants scrutiny. A substantial proportion of existing studies have employed pre-Sepsis-3 diagnostic criteria; many have small sample sizes and rely on unadjusted single-variable comparisons without controlling for disease severity or comorbidity burden, thereby precluding adequate adjustment for confounding. No multivariable analysis specific to a Turkish ICU population currently exists.

This study aimed to evaluate the independent effect of obesity on CRP and PCT levels at the time of sepsis diagnosis in ICU patients meeting Sepsis-3 criteria, using multivariable regression analysis adjusted for disease severity and comorbidity burden.

Materials and methods

Study design and patient selection

This retrospective, single-centre observational study was conducted at the Ondokuz Mayıs University Mikail Yüksel Intensive Care Unit between January 2025 and December 2025. Adult patients aged 18 years or older who were admitted to the ICU with a diagnosis of sepsis or who developed sepsis during their ICU stay were included. Sepsis was diagnosed in accordance with the Sepsis-3 consensus definition, based on a ≥2-point increase in the Sequential Organ Failure Assessment (SOFA) score in the presence of suspected infection (1).

Inclusion criteria were: (i) age ≥18 years; (ii) diagnosis of sepsis according to Sepsis-3 criteria; (iii) availability of CRP and procalcitonin measurements at the time of sepsis diagnosis; and (iv) availability of height and weight data for BMI calculation. Exclusion criteria were: (i) age <18 years; (ii) pregnancy; (iii) active malignancy; (iv) missing BMI or primary biomarker data; and (v) for patients with recurrent ICU admissions during the same hospitalisation, all records other than the first admission. All patients enrolled in the study were consecutive cases meeting the inclusion criteria during the specified period; no exclusions based on formal sample size calculations were made, and all eligible patients were included in the analysis. The patient selection process is illustrated in Figure 1.

The study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (approval no: 2025/712). Informed consent was waived owing to the retrospective study design. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection and variables

Demographic data, comorbidity information, and clinical parameters were obtained from patient records.

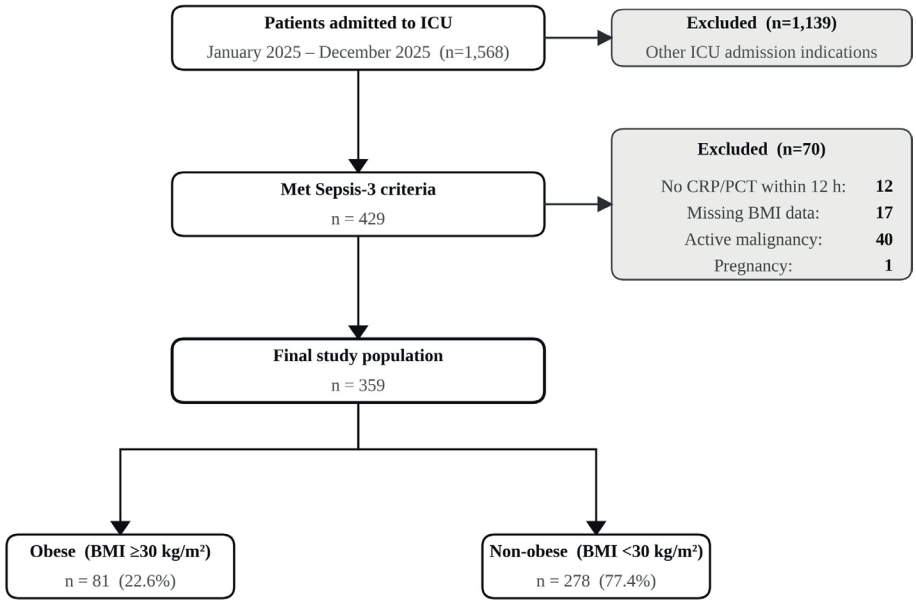

Figure 1. Patient selection flowchart.

BMI: body mass index; CRP: C-reactive protein; PCT: procalcitonin; ICU: intensive care unit.

Patients were classified into two groups based on BMI: non-obese (BMI < 30 kg/m²) and obese (BMI ≥ 30 kg/m²). This cut-off was determined in accordance with the World Health Organization's international BMI classification (10). BMI was calculated using height and weight values measured by the attending physician at the time of ICU admission and recorded in the patient's medical file; these values were retrieved retrospectively from patient records [BMI = weight (kg) / height² (m²)]. Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI) (11). The degree of organ dysfunction was determined by the SOFA score recorded at the time of sepsis diagnosis (12).

The primary outcomes were serum CRP (mg/L) and procalcitonin (ng/mL) levels measured at the time of sepsis diagnosis. Secondary outcomes were ICU mortality and ICU length of stay. CRP and procalcitonin were measured within the first 12 hours following the diagnosis of sepsis, while lactate and creatinine values were obtained at the time of diagnosis as part of routine clinical care.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test; as distributions were skewed, continuous variables are presented as median (interquartile range, IQR). Categorical variables are expressed as numbers and percentages.

Between-group comparisons for continuous variables were performed using the Mann–Whitney U test, and categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. The independent effect of obesity on CRP and procalcitonin levels was assessed using multivariable linear regression, adjusted for age, sex, SOFA score, and CCI. Logarithmic transformations were applied to CRP and procalcitonin owing to their right-skewed distributions; results are reported as exponentiated coefficients (exp (β)) with 95% confidence intervals (95% CI). A p-value of <0.05 was considered statistically significant.

This observational cohort study was prepared and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline.

Results

A total of 359 patients with sepsis were included; 81 (22.6%) were classified as obese and 278 (77.4%) as non-obese. No statistically significant difference was observed between the two groups with respect to age [70.0 (61.0–77.0) vs. 69.0 (56.0–78.0) years; p=0.536], CCI [7.0 (5.0–9.0) vs. 7.0 (5.0–9.0); p=0.723], or SOFA score [9.0 (5.0–13.0) vs. 10.0 (7.0–12.0); p=0.537]. Male sex was significantly more prevalent in the non-obese group (61.9% vs. 29.6%; p<0.001). Baseline clinical and laboratory characteristics of both groups are presented in Table 1.

Although the primary outcomes — CRP and procalcitonin levels — were numerically higher in the obese group, no statistically significant between-group difference was observed [CRP: 145.0 (70.0–239.0) vs. 112.0 (48.0–191.0) mg/L; p=0.135, and procalcitonin: 2.1 (0.5–12.8) vs. 1.5 (0.4–6.9) ng/mL; p=0.260]. In the multivariable regression analysis, after adjustment for age, sex, SOFA score, and CCI, obesity was not independently associated with either CRP (expβ 1.16; 95% CI 0.86–1.56; p=0.321) or procalcitonin (expβ 1.49; 95% CI 0.88–2.51; p=0.136) levels. In the same model, SOFA score emerged as an independent and robust predictor of both CRP (expβ 1.06; 95% CI 1.03–1.09; p<0.001) and procalcitonin (expβ 1.26; 95% CI 1.20–1.32; p<0.001) (Table 2).

Regarding secondary outcomes, ICU mortality was comparable between the obese and non-obese groups (63.0% vs. 68.3%; p=0.439). The high mortality rates observed in both groups were consistent with the median SOFA score of 9–10 in this cohort, reflecting the critical illness severity of the study population. No significant difference in ICU length of stay was identified [9.0 (5.0–16.0) vs. 8.0 (5.0–14.0) days; p=0.717]. Lactate levels were similar in both groups [2.1 (1.5–2.9) vs. 2.1 (1.4–3.3) mmol/L; p=0.917], whereas creatinine levels were significantly higher in the obese group [2.0 (1.2–3.0) vs. 1.4 (0.9–2.6) mg/dL; p=0.006]. The sex distribution differed markedly between the two groups; male sex was substantially more prevalent in the non-obese group compared with the obese group (61.9% vs. 29.6%; p<0.001). This imbalance reflects the higher likelihood of women meeting the BMI ≥30 kg/m² threshold, and the unequal distribution of male and female patients across both groups constitutes a demographic constraint that must be considered when interpreting outcomes shaped by sex interactions, such as the obesity paradox.

Table 1. Baseline demographic, clinical and laboratory characteristics of patients.

Variable	All patients (n=359)	Obese (n=81)	Non-obese (n=278)	p
Age, years – median (IQR)	69.0 (58.0–77.0)	70.0 (61.0–77.0)	69.0 (56.0–78.0)	0.536
Male sex – n (%)	196 (54.6%)	24 (29.6%)	172 (61.9%)	<0,001
BMI, kg/m² – median (IQR)	26.0 (22.9–29.4)	33.1 (31.2–36.3)	24.2 (22.0–27.1)	–
Charlson Comorbidity Index – median (IQR)	7.0 (5.0–9.0)	7.0 (5.0–9.0)	7.0 (5.0–9.0)	0.23
SOFA score – median (IQR)	9.5 (6.0–12.0)	9.0 (5.0–13.0)	10.0 (7.0–12.0)	0.537
CRP, mg/L – median (IQR)	117.0 (50.0–199.0)	145.0 (70.0–239.0)	112.0 (48.0–191.0)	0.135
Procalcitonin, ng/mL – median (IQR)	1.6 (0.4–8.1)	2.1 (0.5–12.8)	1.5 (0.4–6.9)	0.260
Lactate, mmol/L – median (IQR)	2.1 (1.4–3.3)	2.1 (1.5–2.9)	2.1 (1.4–3.3)	0.917
Creatinine, mg/dL – median (IQR)	1.6 (0.9–2.7)	2.0 (1.2–3.0)	1.4 (0.9–2.6)	**0.006**
ICU length of stay, days – median (IQR)	8.0 (5.0–15.0)	9.0 (5.0–16.0)	8.0 (5.0–14.0)	0.717
ICU mortality – n (%)	241 (67.1%)	51 (63.0%)	190 (68.3%)	0.439

IQR: interquartile range; BMI: body mass index; CRP: C-reactive protein; ICU: intensive care unit.
Mann-Whitney U test was used for continuous variables and chi-square test for categorical variables.

Table 2. Multivariable regression analysis of the association between obesity and CRP and procalcitonin levels.

Variable	CRP — expβ (95% CI)	p	Procalcitonin — expβ (95% CI)	p
Obesity (reference: non-obese)	1.16 (0.86–1.56)	0.321	1.49 (0.88–2.51)	0.136
Age (per year)	1.00 (0.99–1.01)	0.953	0.99 (0.97–1.00)	0.080
Male sex (reference: female)	1.03 (0.81–1.30)	0.815	0.91 (0.60–1.38)	0.663
SOFA score (per point)	1.06 (1.03–1.09)	**<0.001**	1.26 (1.20–1.32)	**<0.001**
Charlson Comorbidity Index (per point)	1.03 (0.99–1.07)	0.179	1.00 (0.92–1.07)	0.914

CI: confidence interval; CRP: C-reactive protein; CCI: Charlson Comorbidity Index; SOFA: Sequential Organ Failure Assessment.
Dependent variables were log-transformed; coefficients are presented as expβ. The model was adjusted for obesity, age, sex, SOFA score, and CCI.

The results of the ROC analysis for the ability of CRP and procalcitonin to predict ICU mortality in the overall patient cohort are presented in Table 3. The AUC for CRP was 0.666 (95% CI 0.606–0.729), and for procalcitonin, 0.691 (95% CI 0.632–0.754). The optimal threshold values determined by the Youden index were ≥137 mg/L for CRP (sensitivity 53.5%, specificity 73.7%) and ≥0.9 ng/mL for procalcitonin (sensitivity 71.8%, specificity 59.3%). In subgroup analyses, the optimal CRP threshold in the obese group was ≥145 mg/L, compared with ≥67 mg/L in the non-obese group; the corresponding procalcitonin thresholds were ≥0.52 ng/mL and ≥1.26 ng/mL, respectively. This difference in CRP thresholds is clinically noteworthy: the mortality signal threshold in obese patients was more than twice that in their non-obese counterparts, suggesting that the chronic inflammatory background associated with adipose tissue may cause CRP to reflect a mortality signal only at substantially higher levels. Nevertheless, AUC differences between the two groups were not statistically significant on DeLong testing for either CRP ($Z=0.477$; $p=0.633$) or procalcitonin ($Z=-0.036$; $p=0.971$). Spearman correlation coefficients between BMI and CRP ($r=0.067$; $p=0.202$) and between BMI and procalcitonin ($r=0.046$; $p=0.388$) were also non-significant. ROC curves for both groups are presented in Figure 2.

Post-hoc power analysis revealed that the observed effect sizes (Cohen's $d=0.219$ for CRP and $d=0.165$ for procalcitonin) were substantially below the threshold for clinical meaningfulness ($d=0.355$). This finding suggests that the relationship between obesity and these inflammatory biomarkers is of limited clinical significance, rather than indicating an undetected effect in the current sample.

Table 3. ROC analysis results for CRP and procalcitonin in predicting ICU mortality.

Group / Biomarker	AUC	95% CI	Optimal threshold	Sensitivity	Specificity
All patients (n=359)					
CRP	0.666	0.606–0.729	≥137 mg/L	%53.5	%73.7
Procalcitonin	0.691	0.632–0.754	≥0.9 ng/mL	%71.8	%59.3
Obese group (n=81)					
CRP	0.696	0.569–0.797	≥145 mg/L	%64.7	%73.3
Procalcitonin	0.690	0.570–0.802	≥0.52 ng/mL	%84.3	%53.3
Non-obese group (n=278)					
CRP	0.661	0.598–0.730	≥67 mg/L	%73.2	%52.3
Procalcitonin	0.695	0.624–0.758	≥1.26 ng/mL	%64.2	%68.2

AUC: area under the curve; CI: confidence interval; CRP: C-reactive protein.
95% CI calculated using the bootstrap method (1,000 iterations). Optimal threshold values were determined using the Youden index for the overall cohort and each subgroup separately. AUC differences between obese and non-obese groups were assessed by DeLong test: CRP p=0.633, procalcitonin p=0.971. Caution is advised when interpreting subgroup analyses owing to small sample sizes.

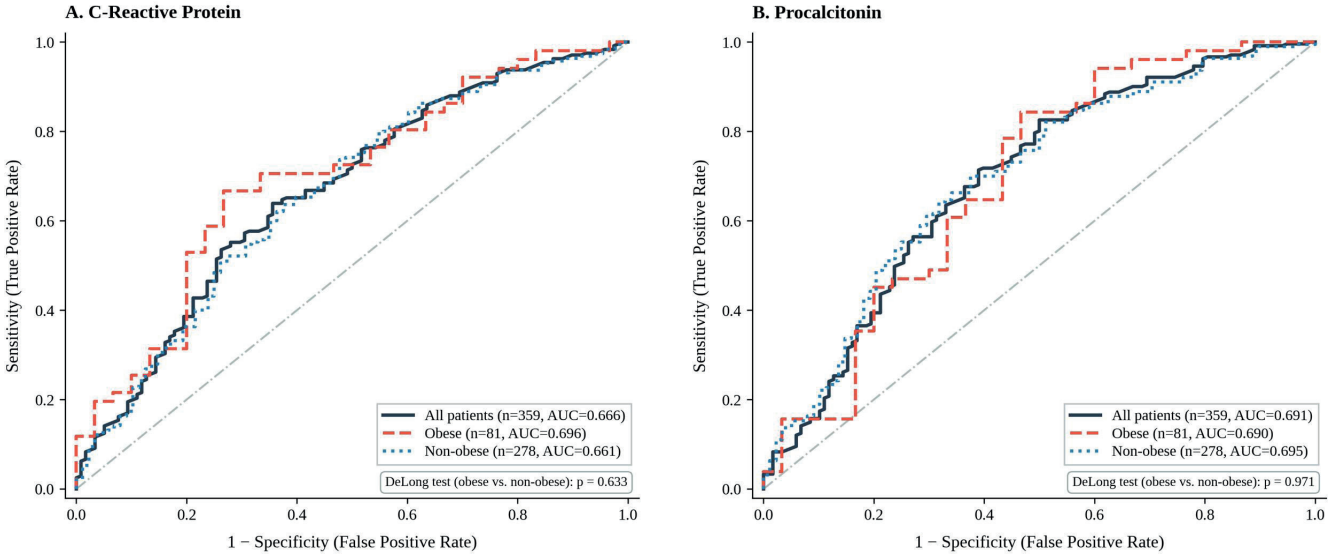

Figure 2. ROC curves for CRP and procalcitonin in predicting ICU mortality in obese and non-obese patients with sepsis.

AUC: area under the curve; CRP: C-reactive protein; ICU: intensive care unit; PCT: procalcitonin.

ROC curves are shown for all patients (solid black line), obese patients (dashed red line), and non-obese patients (dotted blue line). The diagonal dashed grey line represents the reference line of no discrimination. AUC differences between obese and non-obese groups were assessed by DeLong test: CRP p=0.633, procalcitonin p=0.971.

Discussion

This study investigated the relationship between obesity and early inflammatory biomarkers in 359 ICU patients diagnosed with sepsis according to Sepsis-3 criteria. Although CRP and procalcitonin levels were numerically higher in the obese group, obesity was not identified as an independent predictor of either biomarker in multivariable analysis adjusted for age, sex, SOFA score, and CCI. This negative finding constitutes the principal result of our study. It suggests that the relationship between obesity and these inflammatory biomarkers is of limited clinical magnitude, largely overshadowed by the dominant effect of disease severity. The variable that emerged as the strongest independent predictor of both biomarkers in the multivariable model was the SOFA score — a surrogate of disease severity. No significant difference in the prognostic value for mortality prediction was observed between obese and non-obese groups in the ROC analysis; ICU mortality, length of stay, and lactate levels were also comparable. However, creatinine levels were significantly higher in the obese group.

The relationship between obesity and inflammation has long been established. Adipose tissue functions as a metabolically active endocrine organ that continuously secretes pro-inflammatory adipokines, principally interleukin (IL)-6, tumour necrosis factor-alpha (TNF-α), and leptin, establishing a state of chronic low-grade inflammation associated with obesity. Visser et al. demonstrated a positive correlation between BMI and CRP levels in a large population-based study and reported elevated baseline CRP levels in obese individuals (4). Abbasi et al. showed that even procalcitonin values within the normal range were positively associated with BMI and waist circumference, and that obesity, insulin resistance, and the metabolic syndrome significantly elevated procalcitonin levels (7). This pathophysiological basis supports the hypothesis that obese patients with sepsis might be expected to exhibit higher CRP and procalcitonin levels.

Direct evidence on this topic in the literature remains sparse. Simon et al. examined 243 consecutive patients treated for severe sepsis or septic shock according to SCCM criteria in the ICUs of two university hospitals, and reported higher procalcitonin and CRP values in patients with BMI ≥30 kg/m^2; however, the difference in log-transformed procalcitonin only approached borderline significance (p=0.052) (6). The relationship was particularly pronounced in patients with positive blood cultures, and the authors emphasised the need for more detailed investigation of adipose tissue's role in severe sepsis. Abbasi et al. further demonstrated that obesity, insulin resistance, and the metabolic syndrome independently elevated procalcitonin levels in analyses stratified by metabolic phenotype (7), highlighting the influence of metabolic context on biomarker values in the pre-Sepsis-3 era. In our study, examining a cohort meeting Sepsis-3 criteria and substantially greater disease severity, a similar numerical trend was observed. Yet, obesity did not emerge as an independent determinant in the multivariable analysis. Two explanations may account for this discrepancy: first, the suppressive effect of disease severity on the inflammatory response may be considerably stronger in cohorts defined by Sepsis-3 criteria; second, the pure effect of obesity — disentangled from metabolic comorbidities — may be too small to detect at the current sample size.

In our multivariable analysis, the SOFA score emerged as the strongest independent predictor of both CRP (expβ 1.06; 95% CI 1.03–1.09; p<0.001) and procalcitonin (expβ 1.26; 95% CI 1.20–1.32; p<0.001). This finding is directly aligned with the conceptual framework established by the Sepsis-3 consensus definition, in which the SOFA score serves as the operational criterion for organ dysfunction (1). It is well established that both the hepatic acute-phase response and procalcitonin release increase in proportion to the degree of organ dysfunction; consequently, the independent effect of SOFA on inflammatory biomarkers is a biologically expected finding (1). Our data corroborate the SOFA score's role not only as a predictor of mortality but also as an independent determinant of inflammatory biomarker levels, further suggesting that the obesity-related inflammatory background is relatively attenuated in the face of acute organ dysfunction signals.

The ROC analysis in our study demonstrated that CRP and procalcitonin predicted mortality with comparable accuracy in both groups; the AUC was 0.666 for CRP and 0.691 for procalcitonin. AUC differences between the groups were not statistically significant on DeLong testing (p=0.633 and p=0.971, respectively). These findings are consistent with large-scale studies documenting the limited prognostic performance of CRP and procalcitonin in predicting sepsis mortality. In a multicentre study of 1,772 patients with septic shock based on the Korean Shock Society registry, both biomarkers were elevated in non-survivors. Yet, neither was an independent prognostic predictor in multivariable analysis (13). Similarly, a recent study by Schupp et al. reported poor prognostic AUC values for CRP and procalcitonin about 30-day all-cause mortality in patients with sepsis and septic shock (14). In this context, the Youden threshold analysis yields a clinically noteworthy finding: the optimal CRP mortality threshold in the obese group was ≥145 mg/L, compared with ≥67 mg/L in the non-obese group. Although this AUC difference did not reach statistical significance, the disparity in thresholds suggests that, owing to the chronic inflammatory background derived from adipose tissue, CRP may only begin to carry a mortality signal at substantially higher levels in obese patients.

The most prominent secondary outcome was significantly higher creatinine levels in the obese group (p=0.006). This finding is consistent with the recent study by Ahn et al., published in JAMA Network Open, involving 4,041 patients with sepsis, which demonstrated that obesity is an independent risk factor for early sepsis-associated acute kidney injury (SA-AKI) and that its development adversely affects clinical outcomes (15). The adverse renal effects of obesity are multifactorial and include glomerular hyperfiltration, insulin resistance-mediated

tubular injury, activation of the renin-angiotensin-aldosterone system, and direct nephrotoxic effects of pro-inflammatory cytokines derived from adipose tissue. Furthermore, the relatively lower muscle mass in obese patients may undermine creatinine as an adequate reflection of renal dysfunction. This methodological limitation warrants systematic evaluation of the creatinine findings from our study in larger patient series.

About the obesity paradox, ICU mortality in our study was similar between the obese and non-obese groups (63.0% vs. 68.3%; p=0.439). This finding is consistent with the conflicting evidence in the ICU mortality literature about obesity. Yeo et al., in a multicentre prospective Korean cohort of 6,424 patients with sepsis, reported significantly higher in-hospital mortality in the non-obese group compared with the obese group on matched analysis (36.7% vs. 25.3%; p<0.001), attributing this to the classical obesity paradox (8). The meta-analysis by Gao et al. demonstrated that obesity was associated with lower sepsis mortality (OR=0.82; 95% CI 0.69–0.97); however, the authors noted that this protective effect appeared to be less robust in ICU settings and in prospective cohorts (16). Zhang et al., in a large-scale analysis of the MIMIC-IV database, demonstrated that the protective effect of obesity in sepsis varied markedly by age and sex, being most pronounced in elderly male patients (3). In our study, the substantially higher proportion of women in the obese group (70.4%) emerges as a demographic constraint that limits the comparability of the two groups in the context of the obesity paradox. This sex disparity most likely reflects the pattern inherent to BMI-based obesity classification: men more frequently exhibit central obesity and may fall below BMI cut-offs in some populations.

This study has several methodological strengths. The systematic application of the Sepsis-3 definition eliminates the diagnostic heterogeneity observed in many earlier studies. Enrolling consecutive patients who meet the inclusion criteria throughout the study period reduces selection bias. The multivariable analytical design minimises confounding inherent to previously published univariable comparisons and enables a more reliable estimation of the independent effect of obesity. Given the paucity of Sepsis-3 cohort data from Turkey, this study makes an original contribution to the regional literature.

Conversely, the study should be interpreted in light of its limitations. The retrospective, single-centre design limits generalisability compared with prospective multicentre studies. Post-hoc power analysis revealed that the observed effect sizes (Cohen's d=0.219 for CRP and d=0.165 for procalcitonin) were substantially below the pre-specified clinical threshold. At the same time, this supports the biological plausibility of the negative finding, but it does not entirely exclude the possibility of a type II error. BMI does not fully reflect the quantity or distribution of visceral adipose tissue; future studies incorporating complementary measures such as waist circumference or abdominal computed tomography are recommended to investigate this relationship in greater detail. The markedly higher proportion of women in the obese group (70.4%) limits the comparability of the two groups from a sex-balance perspective, particularly requiring careful interpretation of outcomes involving sex interactions. Finally, the inability to incorporate culture data and the primary infection focus into the analysis restricted the evaluation of pathogen-specific differences in biomarker responses.

Conclusion

This study demonstrates that obesity does not independently affect CRP and procalcitonin levels in ICU patients diagnosed with sepsis according to Sepsis-3 criteria. Although both inflammatory biomarkers were numerically higher in the obese group, this difference lost statistical significance following adjustment for the SOFA score — a key indicator of disease severity. In the multivariable analysis, the strongest independent predictor of CRP

and procalcitonin was the SOFA score rather than obesity. While ICU mortality, length of stay, and lactate levels were comparable between groups, significantly elevated creatinine levels in obese patients suggest that obesity may impose an additional burden on renal function during the course of sepsis. The ROC analysis demonstrated that the prognostic value of CRP and procalcitonin for mortality prediction was independent of obesity status, with no statistically significant difference between the two groups. These findings suggest that, in the context of sepsis, obesity alone is not a decisive determinant in the interpretation of inflammatory biomarkers; the primary determinant is the clinical expression of organ dysfunction. Prospective, multicentre studies with larger sample sizes investigating whether this relationship varies with disease severity will provide more definitive guidance for the clinical use of sepsis biomarkers.

Ethical approval

This study has been approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (approval date: 10.09.2024, number: 2025/712). Informed consent was not obtained due to the retrospective design of the study.

Author contribution

Study conception and design: ÖYÇ, Mİ, FÜ; data collection: Mİ, TSA, NÜA; analysis and interpretation of results: ÖYÇ, NÜA, FÜ; draft manuscript preparation: ÖYÇ, Mİ, FÜ. The authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

Generative AI statement

During the preparation of this work, the author(s) utilized Claude (Anthropic) to check grammar and sentence structure in the English manuscript text. After carefully reviewing and editing the content as necessary, full responsibility for the publication's content is taken by the author(s). This incorporation of AI tool usage primarily affected language editing; data collection, analysis, and interpretation were performed entirely by the authors.

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ORIGINAL RESEARCH

Incidence and risk factors of acute kidney injury after hip fracture surgery in oldest old patients

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ABSTRACT

Objective: Acute kidney injury (AKI) is a critical clinical event after hip fracture operation. Our study aimed to determine risk factors and the incidence of postoperative AKI among patients ≥ 85 years who underwent hip fracture surgery and were admitted to an intensive care unit (ICU).

Methods: The medical data of all patients ≥ 85 years that underwent hip fracture surgery were retrospectively analyzed.

Results: During the study period, 164 patients were analyzed and had a mean age of 89.6 ± 3.5 years, including 122 females (74.4%). The incidence of postoperative AKI was 26.8% and 26.2% were Stage I. Preoperative hypertension, usage of diuretics, preoperative lymphopenia, low heart rate upon ICU admission, high sequential organ failure assessment scores on postoperative 1st, 2nd, and 3rd days and low MAP on the postoperative 2nd day were determined independent risk factors about AKI after operation.

Conclusion: The incidence of AKI was 26.8%. Preoperative hypertension, use of diuretics, preoperative lymphopenia, low heart rate at intensive care unit admission, high sequential organ failure assessment scores on postoperative 1st, 2nd, and 3rd days, and low MAP on postoperative 2nd day were independent risk factors about AKI after hip fracture operations in the oldest-old patients.

Keywords: acute kidney injury, hip fracture, surgery, intensive care unit, old age

Introduction

As someone's age increases, there is decreased bone-muscle mass and bone density, increased mineral loss, shortened stature, loss of flexibility and bending in the spine, and degeneration of the joints. As a result of these changes, fractures, kyphosis, back pain, tension in the joints, loss of flexibility, pain, balance disorder, osteoporosis, degenerative arthritis, and falls may be seen in the elderly population. The incidence of elderly people undergoing hip fracture operation is increasing with the aging of the world's population (1,2). It is predicted that the number of patients undergoing hip surgery due to fractures may double by 2050, depending on the prolongation of the expected life expectancy and advances in medicine (1,2).

Acute kidney injury (AKI) is a clinical situation characterized by rapid deterioration in glomerular filtration and is also a common complication in critically ill elderly patients. The reported incidence of AKI in old patients was between 15.3–60% after hip fracture operation (2-6). The incidence of AKI is as high as 57.3% among patients admitted to an intensive care unit (ICU), and the need for renal replacement therapy occurs in approximately 10% of these patients (7,8). Approximately 13.3 million cases worldwide are

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diagnosed with AKI every year, and the mortality rate of AKI is estimated to be approximately 1.7 million (9,10).

Age-related changes in renal function, multiple comorbidities, hospitalization, surgery, preoperative clinical conditions, intraoperative events, and various complications during a postoperative period may increase the incidence of AKI in older individuals (3,4,6,11,12). There is a lack of data on the risk factors and incidence of AKI in postoperative period, especially in oldest-old patients.

This present study purposed to research the risk factors and incidence for postoperative AKI among patients ≥ 85 years old who were performed hip fracture surgery being admitted to a surgical ICU, retrospectively.

Materials and methods

The medical data of all patients ≥ 85 years old who underwent hip fracture surgery between April 4, 2011 and September 1, 2021 were retrospectively analyzed. AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines based on urine output and serum creatinine (13). The patients were divided into two groups: non-AKI and AKI.

There are different classifications that group old people according to age. In some studies, the youngest - old are those between 65 and 74 years old, the middle-old those between 75 and 84 years old, and the oldest old are those ≥ 85 years old (14). We included the oldest-old patients in this study according to this grouping.

The primary aim of this study was to analyze the incidence and risk factors associated with postoperative AKI after hip fracture surgery in elderly patients ≥ 85 years. The secondary aim was to state the length of ICU and hospital stays and mortality rates.

Data collection and definitions

Medical records of patients were collected from digital nursing, anesthesia follow-up, and medical data during preoperative, intraoperative, and postoperative periods : gender, age, and body mass index, comorbidities, hypertension (HT), coronary artery disease (CAD), diabetes mellitus (DM), and preoperative period data: drugs (angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drug (NSAIDs), angiotensin converting enzyme inhibitors (ACEIs)], functional status, left ejection fraction (EF), emergency or elective surgery, types of fractures and surgery, the American Society of Anaesthesiologists (ASA) score, intraoperative period data: type of anesthesia, duration of surgery, type and volume of blood and blood products transfused, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), presence of bradycardia, glucose, lactate, usage of ephedrine/norepinephrine/atropine/tranexamic acid, amount and type of fluid used, arterial blood gas values, postoperative period data: type and volume of blood and blood products transfused, usage of ephedrine/norepinephrine/atropine/tranexamic acid, amount and type of fluid usage, model- dose of vasopressor or inotrope, vital signs, the Glasgow coma score (GCS), the sequential organ failure assessment (SOFA) score (on postoperative first third days), the Acute Physiology and Chronic Health Evaluation System (APACHE II) score at ICU admission and postoperative first three days; arterial blood gas (ABG) values, lactate value (intraoperative and postoperative), laboratory values (preoperative and postoperative), presence of AKI, AKI stage and length of hospital-ICU stay, and mortality rates of ICU-hospital (30 days).

Patients younger than 85 years, who underwent other orthopedic surgeries without hip fracture surgery, whose data could not be available, who were diagnosed with chronic renal failure, and who underwent routine hemodialysis were excluded from this study.

Statistical analysis

The Statistical Package for the Social Sciences 25.0 (Version 25.0; SPSS Inc., Chicago, IL, USA) was used. Frequencies were presented as percentages (%) and numbers (n). The variables were presented as mean values ± standard deviations. Categorical variables between the two groups were analyzed by the chi-square test. In the comparison of nonparametric continuous variables, Mann-Whitney test and independent sample t-test were used for quantitative data analysis, and qualitative data analysis was analyzed by Fisher's exact and chi-square test. The univariate and multivariate logistic regression analyses were used for factors affecting AKI after hip surgery ($p<0.05$ was considered statistically significant).

Results

During the study period, hip surgery was performed on 290 patients over the age of 85. One hundred sixty-four of these patients were admitted to the ICU during the postoperative period (Figure 1). Of the 164 patients included in this study, 122 (74.4%) were female, and the mean age was 89.6 ± 3.5 years (between 85–103 years). Forty-four patients (26.8%) had postoperative AKI. Most of the patients (65.2%) were admitted from an emergency service. According to functional status, 135 patients (82.3%) were independent, 20 (12.2%) were partially dependent, and nine (5.5%) were in nursing homes. The most common comorbidity was hypertension (HT) (82.9). HT, CAD, and renal diseases were more common in the AKI group when compared to the non-AKI group (93.2% vs. 79.7% p = 0.02; 38.6% vs. 20.0% p = 0.01, 15.9% vs. 10.0% p = 0.003, respectively). The use of preoperative diuretic drugs was higher in the AKI group when compared to the non-AKI group (22.7% vs. 8.3%, p = 0.01) (Table 1).

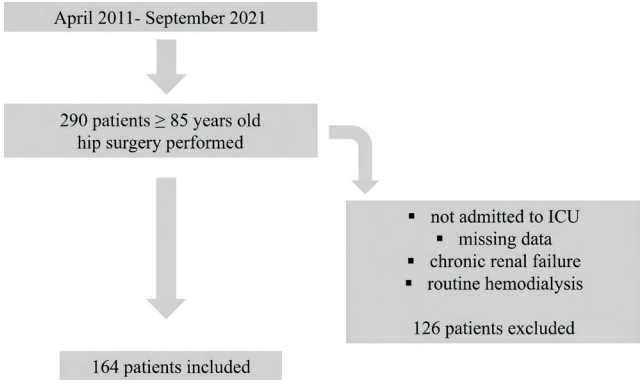

Figure 1. Flowchart of the patients.

Interthoracanteric femur fractures were the most common type of fracture (62.8%). Proximal femoral nail antirotation (PFNA) was the most common type of surgery (64.1%). According to the ASA score, 102 patients (62.2%) had an ASA score of 3. There was not statistically significant difference in terms of fracture/surgery type, use of preoperative antibiotics, and blood/blood product between the groups. Preoperative EF was lower in the AKI group when compared to the non-AKI group (44.7 ± 17.4 vs. 52.4 ± 11.3, p = 0.01) (Table 2).

Spinal anesthesia was the most common used type of anesthesia (81.8%). Ephedrine usage was higher in the non-AKI group than in the AKI group (24.4% vs. 9.1%, p = 0.02). The mean duration of surgery was 151.3 ± 56.7 minutes. SBP was lower in the non-AKI group than the other group (91.0 ± 20.7 mmHg vs. 98.4 ± 22.8 mmHg, p = 0.037) during the intraoperative period. No statistically significant difference was found in terms of intraoperative blood/blood product usage, adrenaline, noradrenaline usage, MAP, and lactate levels between the groups (Table 2).

The mean APACHE II score was 13.7 ± 4.5, the mean GCS score was 14.8 ± 0.8, and the mean SOFA score was 2.5 ± 1.8 at ICU admission. Heart rate per minute was lower in the group with AKI than in the group without AKI (77.5 ± 17.4 vs. 87.6 ± 23.2, p = 0.008) at ICU admission. The SOFA scores on postoperative 1st (2.9 ± 2.8 vs. 2.0 ± 1.6 p = 0.04), 2nd (2.6 ± 2.5 vs. 1.7 ± 1.5 p = 0.01), and 3rd (2.2 ± 2.3 vs. 1.5 ± 1.7 p = 0.01) days were significantly higher in the group with AKI than in the group without AKI. The SBP, DBP, and MAP on the second postoperative day

Table 1. Demographic and clinical characteristics of the oldest old patients (n=164).

Variables	Mean ±SD			
	Total (n:164)	Postoperative AKI (n:44)	Non-AKI (n:120)	p value
Age, years,	89.6±3.5	89.4±3.4	89.7±3.6	0.6
Body Mass Index (kg/m^2)	24.4±4.7	25.0±4.5	24.2±4.8	0.35
	Number (n) /Percent (%)			
Sex				0.5
Male	42 (25.6)	13 (29.5)	29 (24.2)	
Female	122 (74.4)	31 (70.5)	91 (75.8)	
Admission to ICU				0.3
Emergency Room	107 (65.2)	32 (72.7)	75 (62.5)	
Other Wards in Hospital	57 (34.8)	12 (27.3)	45 (37.5)	
Functional State				0.8
Independent	135 (82.3)	36 (81.8)	99 (82.5)	
Partially dependent	20 (12.2)	5 (11.4)	15 (12.5)	
Nursing home	9 (5.5)	3 (6.8)	6 (5.0)	
Comorbidities				
Hypertension	136 (82.9)	41 (93.2)	95 (79.2)	**0.02**
Diabetes Mellitus	43 (26.2)	16 (36.4)	27 (22.5)	0.1
Congestive heart failure	44 (26.8)	15 (34.1)	29 (24.2)	0.2
Coronary Artery Diseases	41 (25.0)	17 (38.6)	24 (20.0)	**0.01**
Valvular Heart Diseases	12 (7.3)	5 (11.4)	7 (5.8)	0.3
Atriall Fibrilattion	53 (32.3)	17 (38.6)	36 (30.0)	0.35
Respiratory Diseases	29 (17.7)	9 (20.5)	20 (16.7)	0.2
Alzheimer	24 (14.6)	4 (9.1)	20 (16.7)	0.3
Malignancy	21(12.8)	7 (15.9)	14 (11.7)	0.3
Renal Diseases	19 (11.6)	7 (15.9)	12 (10.0)	**0.003**
Staying in a Nursing Home	4 (2.4)	1 (2.3)	3 (2.5)	1.0
Preoperatively used drugs				
ACEi/ARBs	28 (17.1)	11 (25.0)	17 (14.2)	0.1
Diuretics	20 (12.2)	10 (22.7)	10 (8.3)	**0.01**
Anticoagulants	69 (42.1)	21 (47.7)	48 (40.0)	0.4
Antiaggregants	76 (46.3)	25 (56.8)	51 (42.5)	0.5
NSAIDs	4 (2.4)	2 (4.5)	2 (1.7)	0.3
Radiocontrasts	4 (2.4)	0 (0.0)	4 (3.3)	0.6

SD: Standart Deviation, AKI: Acute Kidney Injury, ICU: Intensive Care Unit, ACEi: Angiotensin Converting Enzyme Inhibitors, ARBs: , NSAIDs: Non-steroid antiinflamtuary drugs

were significantly lower in the group with AKI when compared to the other group (114.1±15.0 mmHg vs. 120.1 ± 15.0 p = 0.04; 64.8 ± 11.4 mmHg vs. 69.7 ± 9.6 p = 0.01; 80.7 ± 11.3 mmHg vs. 85.8 ± 9.9 p = 0.01, respectively) (Table 3). No statistically significant difference was found in terms of postoperative blood/blood product, noradrenaline, adrenaline, or ephedrine usage between the groups (Table 2).

The length of ICU stay was statistically significantly longer in the group with AKI than the other group (2.7 ± 4.7 vs. 1.6 ± 2.8, p = 0.004). The length of hospital stay before ICU admission and after ICU discharge were similar between the groups. There was no statistically significant difference between the two groups in terms of ICU, hospital, and 30-day mortality rates (Table 3).

Table 2. Preoperative, intraoperative ve postoperative characteristics of the oldest old patients.

Variables	Number (n) /Percent (%)			
	Total (n:164)	Postoperative AKI (n:44)	Non-AKI (n:120)	p value
Surgical Urgency				0.8
Emergency	8 (4.9)	2 (4.5)	6 (5.0)	
Urgent	5 (3.0)	1 (2.3)	4 (3.3)	
Elective	151 (92.1)	41 (93.2)	110 (91.7)	
Types of Fracture				0.1
Subtrochanteric	7 (4.3)	2 (4.5)	5 (4.2)	
Femoral neck	54 (32.9)	20 (45.5)	34 (28.3)	
Interthorachanteric femur	103 (62.8)	22 (50.0)	81 (67.5)	
Types of Surgery				0.7
Total Hip Replacement	5 (3.0)	2 (4.5)	3 (2.5)	
Partial Hip Replacement	54 (32.9)	19 (43.2)	35 (29.2)	
PFNA	105 (64.1)	23 (52.3)	82 (68.3)	
Presence of UTI	10 (6.1)	1 (2.3)	9 (7.5)	0.3
Usage of Antibiotics	13 (7.9)	3 (6.8)	10 (8.3)	1.0
ASA classification				0.8
2	48 (29.3)	12 (27.3)	36 (30.0)	
3	102 (62.2)	28 (63.6)	74 (61.7)	
4	13 (7.9)	4 (9.1)	9 (7.5)	
5	1 (0.6)	0	1 (0.8)	
Usage of Blood/Blood Product	8 (4.9)	4 (9.1)	4 (3.3)	0.2
	Mean±SD			
Peripheral Oxygen Saturation	93.6±5.6	92.7±10.1	93.9±2.2	0.2
Ejection Fraction (%)	50.3±13.6	44.7±17.4	52.4±11.3	**0.01**
	Intraoperative Characteristics			
Type of Anesthesia				0.8
General	25 (15.2)	5 (11.4)	20 (16.7)	
Spinal	134 (81.8)	38 (86.3)	96 (80.0)	
General+Spinal	5 (3.0)	1 (2.3)	4 (3.3)	
PRBCs transfusion	60 (36.6)	18 (41.0)	42 (35.0)	0.4
FFP transfusion	33 (20.1)	11 (25.0)	22(18.5)	0.3
Bradicardia <60 per minute	30 (18.3)	13 (29.5)	17(14.2)	0.08
Tachicardia >100 per minute	20 (12.2)	3 (6.8)	17 (14.2)	0.3
Ephedrine use	33 (20.1)	4 (9.1)	29 (24.4)	**0.02**
Noradrenaline use	16 (9.8)	4 (2.5)	12 (10.1)	1.0
Adrenaline use	1 (0.6)	0 (0.0)	1 (0.8)	1.0
Colloid fluid use	42 (25.7)	9 (20.5)	33 (27.7)	0.4
	Mean±SD			
Duration of Surgery (minute)	151.3±56.7	158.8±60.6	148.6±55.2	0.3
Sistolic Blood Pressure (mmHg)	93.0±21.5	98.4±22.8	91.0±20.7	**0.037**
Diastolic Blood Pressure	49.5±11.8	50.6±13.2	49.1±11.3	0.6
Mean Arterial Pressure	64.0±14.1	66.2±15.7	63.2±13.5	0.25
Glucose (mg/dl)	109.6±34.2	103.7±35.2	112.1±33.7	0.4
Lactate (mmol/L)	2.1±7.9	1.4±0.9	2.4±9.4	0.8
	Postoperative Characteristics			
PRBCs transfusion	39 (23.8)	12 (27.3)	27 (22.5)	0.4
FFP transfusion	7 (4.3)	1 (2.3)	6 (5.0)	0.4
Noradrenaline use	3 (1.8)	1 (2.3)	2 (1.7)	1.0
Adrenaline use	1 (0.6)	1 (2.3)	0 (0.0)	0.3

AKI: Acute Kidney Injury, PFNA: Proximal Femoral Nail Antirotation, UTI: Urinary Tract Infection, SD: Standart Deviation, ASA: The American Society of Anaesthesiologists' classification, PRBCs: Packed Red Blood Cells, FFP: Fresh Frozen Plasma, SD: Standart Deviation.

Table 3. Intensive care unit severity scores, vital signs, length of stay and mortality rates of the oldest old patients.

Variables	Mean±SD			
	Total (n:164)	Postoperative AKI (n:44)	Non-AKI (n:120)	p value
APACHE-II	13.7±4.5	14.4±4.0	13.4±4.7	0.117
GCS	14.8±0.8	14.9±0.7	14.7±0.8	0.213
SOFA (admission)	2.5±1.8	2.8±1.9	2.4±1.9	0.3
Heart rate per minute	84.9±22.2	77.5±17.4	87.6±23.2	**0.008**
MAP (mmHg)	89.1±18.3	87.7±17.6	89.6±18.6	0.5
Lactate (mmol/L)	2.2±2.8	2.1±2.4	2.2±2.9	0.9
SOFA (first day)	2.3±2.0	2.9±2.8	2.0±1.6	**0.04**
MAP	80.2±13.4	77.3±12.4	81.3±13.7	0.1
SOFA (second day)	1.9±1.9	2.6 ±2.5	1.7±1.5	**0.01**
Sistolic Blood Pressure (mmHg)	118.5±15.2	114.1±15.0	120.1±15.0	**0.04**
Diastolic Blood Pressure (mmHg)	68.4±10.3	64.8±11.4	69.7±9.6	**0.01**
MAP	84.4±10.5	80.7±11.3	85.8±9.9	**0.01**
SOFA (third day)	1.7±1.9	2.2±2.3	1.5±1.7	**0.01**
MAP	86.5v9.4	87.4±8.4	86.2±9.8	0.6
Length of Stay (day)				
Before ICU admission	1.6±1.4	1.6±0.9	1.6±1.5	0.7
ICU	1.9±3.5	2.7±4.7	1.6±2.8	**0.004**
After ICU discharge	3.7±3.5	3.7±3.7	3.8±3.5	0.9
Hospital	7.5±5.5	8.1±5.8	7.3±5.4	0.2
Mortality rates (number / percent)				
ICU mortality	6 (3.7)	3 (6.8)	3 (2.5)	0.3
Hospital mortality	10 (6.1)	4 (9.1)	6 (5.0)	0.5
30 days mortality	16 (9.8)	7 (15.9)	9 (7.5)	0.2

SD: Standart Deviation; AKI: Acute Kidney Injury; APACHE II: Acute Physiology and Chronic Health Evaluation System; GCS: Glasgow Coma Scale; SOFA: Sequential Organ Failure Assessment; MAP: Mean Arterial Pressure.

In the AKI group, preoperative lymphocyte levels (1.1 ± 0.5 vs. 2.4 ± 3.8 103/μl, p = 0.019) and prothrombin time (PT) (16.5 ± 13.1 vs. 29.6 ± 15.5 seconds, p = 0.036) were lower when compared to the non-AKI group. The postoperative lymphocyte levels (1.3 ± 1.7 vs. 1.7 ± 2.4 103/μl, p = 0.002) were lower and PTs (16.6 ± 10.5 vs. 14.1 ± 7.1 second, p < 0.001) were higher in the group with AKI compared to the group without AKI (Table 4).

According to a logistic regression analysis, preoperative HT (p = 0.03, OR: 0.274, CI: 95% 0.062–1.208,), diuretics usage (p = 0.01, OR: 0.272, CI: 95% 0.077–0.962), preoperative low lymphocyte level (p = 0.03, OR: 0.274, CI: 95% 0.062-–1.208), low heart rate per minute on ICU admission (p = 0.01, OR: 0.975, CI: 95% 0.951–0.998), high SOFA scores on postoperative 1st, 2nd, and 3rd days (p = 0.01, OR: 1.089, CI: 95% 0.574–2.068; p = 0.007, OR: 1.302, CI: 95% 0.618–2.742; p = 0.01, OR: 1.089, CI: 95% 0.574–2.068), and low MAP on the postoperative 2nd day (p = 0.009, OR: 1.045, CI: 95% 0.919–1.137) after hip fracture operation were independent risk factors about postoperative AKI among oldest-old patients (Table 5).

Table 4. Preoperative and postoperative laboratory values of the oldest old patients.

Variables	Mean±SD			
	Total (n:164)	Postoperative AKI (n:44)	Non-AKI (n:120)	p value
PREOPERATIVE				
Hemoglobin (g/dl)	12.1±8.8	11.2±1.5	12.4±10.2	0.2
Hematocrit (%)	34.9±4.7	34.2±4.6	35.2±4.7	0.3
Lymphocyte (10^3/µl)	2.1±3.4	1.1±0.5	2.4±3.8	**0.019**
BUN (mg/dl)	29.1±13.7	34.3±17.0	27.3±11.9	**0.007**
Creatinine (mg/dl)	1.2±0.7	1.3±0.8	1.1±0.7	**0.001**
Potassium (mg/dl)	4.5±3.3	4.3±0.7	4.5±3.8	0.8
Glucose (mg/dl)	128.2±29.5	130.2±37.0	127.8±28.4	0.9
PT (second)	25.9±131.7	16.5±13.1	29.6±15.5	**0.036**
POSTOPERATIVE				
Hemoglobin (g/dl)	11.0±7.8	10.5±1.6	11.2±9.1	0.5
Hematocrit (%)	30.1±6.6	31.3±7.0	29.7±6.5	0.07
Lymphocyte (10^3/µl)	1.6±2.2	1.3±1.7	1.7±2.4	**0.02**
BUN (mg/dl)	26.1±12.8	30.1±14.0	24.7±12.0	**0.007**
Creatinine (mg/dl)	1.1±0.7	1.2±0.6	1.0±0.7	**0.001**
Potassium (mg/dl)	4.9±6.9	4.3±0.7	5.1±8.1	0.8
Glucose (mg/dl)	136.9±42.7	132.6±35.3	138.3±44.8	0.7
PT (second)	14.8±8.2	16.6±10.5	14.1±7.1	**<0.001**

SD: Standart Deviation; AKI: Acute Kidney Injury; BUN: Blood Urea Nitrogen; PT: Prothrombin Time.

Table 5. Logistic regression model of risk factors for postoperative acute kidney injury.

Risk factors	Odds Ratio	%95 CI	p value
Preoperative Hypertension	0.274	0.062-1.208	**0.03**
Preoperative usage of diuretics	0.272	0.077-0.962	**0.01**
Preoperative lymphopenia	0.274	0.062-1.208	**0.03**
Low heart rate on ICU admission	0.975	0.951-0.998	**0.01**
High SOFA score on first day of ICU admission	1.089	0,574-2,068	**0.01**
High SOFA score on 2nd day of ICU admission	1.302	0,618-2,742	**0.007**
High SOFA score on 3rd day of ICU admission	1.089	0,574-2,068	**0.01**
Low MAP on 2nd day of ICU admission	1.045	0,919-1,137	**0.009**

CI: Confidence Interval; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment; MAP: Mean Arterial Pressure.

Discussion

In the current clinical trial, the incidence of AKI after hip fracture surgery among the oldest-old patients was 26.8%.

The incidence of AKI was between 15.3% and 60% among elderly patients who underwent hip fracture operation in previous studies (2-5). In this current study, the incidence for postoperative AKI after hip fracture operation was 26.8%, as in previous studies. The aging process decreases renal reserve and glomerular filtration rate, impairs renal autoregulation and perfusion, and increases sensitivity to nephrotoxic agents. Increased comorbidities (especially cardiovascular diseases) also cause renal dysfunction. Both physiological and structural changes are associated with AKI in elderly patients (2,12,15).

In our study, HT was more common in the group with AKI when compared to the other group, and preoperative HT was an independent risk factor for the occurence of postoperative AKI. A retrospective cohort study reported a 22% increased risk of having with a blood pressure of >140/90 mmHg in those with AKI compared to those without AKI, after adjusting for some cardiac risk factors and demographic characteristics (16). Hardening, narrowing or weakening of the renal arteries may occur in patient with uncontrolled high blood pressure. Thus, these damaged arteries cannot deliver enough blood to the renal tissue.

When arteries are damaged, necessary nutrients and oxygen cannot reach the nephrons. Thus, the kidneys cannot filter the blood and regulate the balance of water, salts, acids and hormones in the body (17). Previous clinical studies reported that hypertension is a risk factor for AKI (2,3,10,12), and hypertension is also common in patients who have AKI, especially after hip operation, like our results (2,3,18).

In the AKI group of our cohort, we found that CADs and renal disease were more common than in the non-AKI group, as in previous studies (2-4,8,10,19). Atherosclerosis and decreased heart function may be common in patients with preexisting CADs. These clinical conditions increase renal vasoconstriction and decrease renal perfusion, and thus may cause AKI (2,4,10,17-19). Advanced age and surgery may also cause AKI to occur (10,12,15,18).

In the AKI group of our cohort, preoperative usage of diuretic drugs was more common than in the non-AKI group and was an independent risk factor about the occurence of postoperative AKI in our study. Elderly patients have some risk factors that may contribute to the development of AKI, including age-related anatomic and physiologic changes of kidney, increased comorbidity, increased number of drug usage, and changes of medication metabolism (3,4,10,18).

Loop diuretics cause venodilation and diuresis. Thus, it can reduce the effective volume in glomerular filtration rate, renal blood flow and circulation. When loop diuretics are used, acidification of the urine and accumulation of Tamm-Horsfall protein may be increased. Therefore, it is believed that it may cause tubular obstruction (20).

In the AKI group of our cohort, preoperative EF was lower compared to the non-AKI group. Heart failure with low EF or preserved EF leads to impaired myocardial stretchability and decreased cardiac output. Low cardiac output causes decreased renal perfusion, excited sympathetic systems and increased activation of the renin- aldosterone- angiotensin. Thus, water-salt retention increases and causes increased venous congestion. Renal function is worsened by increased renal venous and intra-abdominal pressure (18,21).

When compared to the non- AKI group, heart rate at ICU admission was lower in the AKI group of our cohort, and low heart rate on ICU admission was an independent risk factor about the occurence of postoperative AKI. Bradycardia arrhythmia or tachycardia may temporarily reduce cardiac output; thus, renal autoregulation may be impaired, and renal perfusion may be reduced (22). Low blood volume, such as hypovolemia, decreased cardiac contraction and contraction frequency (heart rate) as a result of heart failure, liver failure, or sepsis, and vascular structures, such as vasculitis, may reduce renal perfusion and cause renal injury (17). Decreased cardiac output with bradycardia reduces renal perfusion and causes AKI.

The SOFA score system include 6 organ systems: coagulation, neurological, renal, cardiovascular, hepatic and respiratory systems. Higher severity scores are expected among patients who have AKI. In the AKI group of our cohort study, the SOFA scores on postoperative 1st, 2nd, and 3rd days were significantly higher compared to the non-AKI group. High SOFA scores on postoperative 1st, 2nd,

and 3rd days were determined as independent risk factors for the occurence of postoperative AKI. Jiang et al. reported that ICU patients with AKI had higher median SOFA scores, and high SOFA scores were independent predictors of mortality (8). In the AKI_EPI study, patients with AKI with a higher Simplified Acute Physiology Score (SAPS) were more severely ill upon admission to the ICU (7). APACHE II, SAPS II, and SOFA scores were accepted as predictors of mortality in elderly patients with AKI. The SOFA score is a useful severity score for predicting the clinical outcomes of patients admitted to the ICU (23).

On the second postoperative day SBP, DBP, and MAP levels were significantly lower in the group with AKI when compared to the other group. Low MAP on the postoperative 2nd day was an independent risk factor about the occurence of postoperative AKI in our cohort. Braüner Christensen et al. reported that SBP/DBP on postoperative days 1 and 2 were significantly lower among patients with AKI after surgery (2). Low blood pressure can cause to decreased renal blood flow and, thus, the occurrence of AKI.

Several studies have shown an association between decreased renal perfusion due to intraoperative hypotension and AKI (23,24). Autoregulation of blood pressure may be impaired among patients with hypertension, chronic renal disease, and atherosclerosis (2,18,23). In a diagnosis of AKI, serum creatinine levels within seven days are evaluated according to KDIGO criteria (4). Thus, hypotension observed on a postoperative 2nd day may cause postoperative AKI. Previous studies presented hypotension as an impotant risk factor for occurrence of AKI in ICU patients, like our findings (17,23).

In the AKI group of our study, preoperative and postoperative lymphocyte levels were lower compared to the non-AKI group, and preoperative lymphopenia was an independent risk factor for the development of postoperative AKI. Each leukocyte subgroup (neutrophil, lymphocyte, monocyte, eosinophil) has a serious role in organ damage and response to injury of inflammation and immunological conditions (24).

It is known that the risk of long-term renal outcomes is associated with the change in leukocyte count. Lymphopenia and monocytopenia in leukopenia may have an association with a higher risk of AKI, whereas neutrophilia in leukocytosis is associated with this risk. Neutropenia and lymphopenia may be associated with higher mortality. T and B lymphocytes cause a natural and adaptive inflammatory response that can lead to the inflammatory process of AKI. Regulatory T lymphocytes are potent immunosuppressive agents. Decreased T lymphocytes may worsen renal dysfunction. Natural killer T cells may play both proinflammatory and protective roles in AKI (25).

The AKI group had prolonged the length of ICU stay compared to the non-AKI group, as in previous studies (3,7,8,12). Among elderly patients with AKI, old age and concomitant comorbidities are risk factors that facilitate the occurence of organ failure. In elderly patients, the natural aging process reduces functional organ reserve. Therefore, risk factors for postoperative AKI may cause organ failures. The need for organ support after acute diseases may be seen in older patients (3). Therefore, the length of stay in hospital and ICU may be long.

Our study has some limitations such as being a retrospective study and a single-center. Therefore, the results cannot be generalized. The data of patients was obtained from digital records.

Conclusion

The incidence for postoperative AKI after hip fracture operation was 26.8% in our cohort study. Preoperative HT, usage of diuretics, preoperative lymphopenia, low heart rate at ICU admission, high SOFA scores on postoperative 1st, 2nd, and 3rd days, and low MAP on postoperative 2nd day were independent risk factors about postoperative AKI after hip fracture operation among the oldest-old patients. Postoperative AKI after hip fracture surgery among patients 85 years and older causes impaired quality of life, prolonged ICU and hospital stay, and increased mortality. The

incidence of postoperative complications and deaths may increase due to decreased vital organs reserves in elderly patients. Any effort to identify relevant risk factors associated with AKI in patients ≥ 85 years old who undergo hip fracture surgery could affect the quality of therapies, improve our understanding of the clinical outcomes, shorten the length of an ICU/hospital stay, and reduce mortality among patients with hip fracture.

Ethical approval

This study has been approved by the Başkent University Institutional Review Board (approval date: 09.03.2022, number: KA22/111). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: FİY, BH, HŞ, PZ; data collection: FİY, BH, HŞ; analysis and interpretation of results: FİY, BH, HŞ, PZ; draft manuscript preparation: FİY, BH, HŞ, PZ. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL RESEARCH

Cumulative drug interaction burden in intensive care patients: association with polypharmacy and clinical outcomes

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ABSTRACT

Objective: Potential drug–drug interactions (pDDIs) are common in intensive care units (ICUs), but whether they independently contribute to adverse clinical outcomes remains unclear because of their close association with polypharmacy. This study evaluated the associations of cumulative pDDI burden and medication burden with clinical outcomes in medical and surgical ICU patients.

Materials and Methods: This retrospective cohort study included 270 adult patients admitted to the medical and surgical intensive care units between January and December 2025. Potential drug–drug interactions were identified using the Lexicomp® database, and the cumulative number of unique pDDIs was calculated for each patient throughout the ICU stay. Multivariable logistic and linear regression analyses were performed to examine the associations of medication burden and cumulative unique pDDI burden with in-hospital mortality, hospital length of stay, and ICU length of stay.

Results: Of the 270 patients, 57.0% were admitted to medical ICUs and 43.0% to surgical ICUs. Patients in medical ICUs had higher APACHE II scores, a greater proportion of high-risk pDDIs, and higher in-hospital mortality than those in surgical ICUs (24.7% vs. 9.5%; $p=0.001$), whereas the total number of medications and the cumulative number of unique pDDIs were similar between the groups. In multivariable analyses, the total number of medications remained an independent predictor of in-hospital mortality and longer hospital and ICU stays. Although the cumulative number of unique pDDIs was associated with in-hospital mortality when evaluated in a separate multivariable model, this association was no longer significant after adjustment for the total number of medications.

Conclusion: Although cumulative pDDI burden was associated with adverse clinical outcomes in univariable analyses, this association was largely explained by overall medication burden. These findings highlight the importance of considering overall medication burden when interpreting the clinical relevance of pDDIs in critically ill patients.

Keywords: drug interactions, intensive care units, polypharmacy, mortality, drug therapy

Introduction

Patients admitted to intensive care units (ICUs) are particularly susceptible to potential drug–drug interactions (pDDIs) because of polypharmacy, acute organ dysfunction, and the complexity of their treatment regimens (1,2). As the number of prescribed medications increases, the risk of clinically relevant drug–drug interactions also rises, which may adversely affect patient outcomes (2,3).

Potential drug–drug interactions (pDDIs) are common in ICUs and have been associated with increased morbidity, longer hospital stays, and higher mortality in previous studies (1,3). However, most previous studies have relied on cross-sectional assessments that capture pDDIs at a single time point. In the ICU, where medication regimens change frequently, the cumulative burden of pDDIs throughout the ICU stay may provide a broader perspective than assessments performed at a single time point (2,4).

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Medical and surgical ICU patients differ in their underlying conditions, treatment approaches, and medication use, which may influence the frequency and cumulative burden of pDDIs (5). However, few studies have directly compared cumulative pDDI burden between these two ICU populations.

In this study, we aimed to evaluate the associations of cumulative pDDI burden and medication burden with clinical outcomes in medical and surgical ICU patients and to determine whether the association between pDDIs and clinical outcomes is independent of overall medication burden.

Materials and methods

Study design

This retrospective cohort study was conducted in the medical and surgical intensive care units of a tertiary care hospital. Medical records of patients admitted between January 1 and December 31, 2025, were retrospectively reviewed.

Patient selection

Adult patients (≥18 years) admitted to the medical or surgical ICU between January 1 and December 31, 2025, who remained in the ICU for at least 24 hours were eligible for inclusion. Patients were classified according to the type of ICU to which they were admitted (medical or surgical). Patients with fewer than two prescribed medications or incomplete medication or clinical data were excluded.

Ethical approval

The study was approved by the Ethics Committee of Aksaray University Faculty of Health Sciences (approval date: March 5, 2026; approval number: 2026/78). The study was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective study design.

Data collection

Demographic data (age, sex), clinical variables (APACHE II score, mortality, ICU and hospital length of stay), and treatment-related variables (total number of medications, vasopressor use) were obtained from patient records and the electronic hospital database.

Medication data were retrospectively extracted from electronic physician order records in the hospital information system. All prescribed medications recorded during the ICU stay, including medications prescribed on an as-needed (PRN) basis, were evaluated for potential drug–drug interactions.

Assessment of drug–drug interactions

Potential drug–drug interactions (pDDIs) were identified using the Lexicomp® Drug Interactions database (version accessed in April 2026). Medications were entered using their generic names, and combination products were evaluated according to their individual active ingredients. Inhaled medications were included. Intravenous fluids, electrolyte solutions, nutrition products, and blood products were excluded because they were outside the predefined scope of medication exposure assessed in this study. All identified pDDIs were independently reviewed by two investigators, and any disagreements were resolved by consensus. Interactions were classified into the following Lexicomp® risk categories: A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy modification), and X (avoid combination).

For the cumulative analysis, each unique drug pair was counted only once regardless of interaction direction. However, the same drug pair was counted separately if it was assigned different Lexicomp® risk categories. Only interactions classified as categories B, C, D, and X were included in the analyses. Category A was excluded because it indicates the absence of a known drug–drug interaction rather than a potential interaction.

Derived variables

The following derived variables were calculated to characterize the cumulative burden of pDDIs during the ICU stay:

- **Cumulative number of unique pDDIs:** The cumulative number of unique pDDIs identified during the ICU stay. Drug pairs assigned to different Lexicomp® risk categories were counted separately.
- **High-risk pDDI ratio:** The proportion of interactions classified as category D or X among all identified pDDIs. This ratio was calculated only for patients with at least one identified pDDI.

Formula:

High-risk pDDI ratio = (Number of D + X interactions) / Total number of unique pDDIs

- **High-risk pDDI count:** The cumulative number of interactions classified as Lexicomp® category D or X during the ICU stay.
- **Presence of at least one high-risk pDDI:** Patients were additionally classified according to whether they had at least one category D or X interaction during the ICU stay.

Statistical analysis

Continuous variables were assessed for normality using histograms and the Shapiro–Wilk test. As most variables were not normally distributed, continuous variables were expressed as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test.

To identify factors independently associated with in-hospital mortality, three multivariable logistic regression models were constructed. Model 1 included age, APACHE II score, vasopressor use, and the total number of medications. Model 2 included age, APACHE II score, vasopressor use, and the cumulative number of unique pDDIs. Model 3 included age, APACHE II score, vasopressor use, the total number of medications, and the cumulative number of unique pDDIs to evaluate their independent associations with in-hospital mortality.

Hospital length of stay and ICU length of stay were analyzed using the same modeling strategy with multivariable linear regression. For each outcome, three separate models were constructed corresponding to those described above. All multivariable regression models were fitted using the Enter method

Multicollinearity among independent variables was assessed using variance inflation factors (VIFs), and VIF values <3 were considered indicative of the absence of problematic multicollinearity. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Comparison of medical and surgical ICU patients

The demographic, clinical, and pDDI-related characteristics of patients according to ICU type are presented in Table 1. Patients admitted to the medical ICU were significantly older than those admitted to the surgical ICU (median age, 75.5 vs. 63.0 years; $p<0.001$) and had higher APACHE II scores (median, 17 vs. 14; $p<0.001$). Vasopressor therapy was used more frequently in the medical ICU group than in the surgical ICU group (22.1% vs. 12.1%; $p=0.033$). Similarly, in-hospital mortality was significantly higher among medical ICU patients (24.7% vs. 9.5%; $p=0.001$).

The total number of medications and the cumulative number of unique pDDIs were comparable between the two groups (both p>0.05). However, medical ICU patients had a higher high-risk pDDI ratio than surgical ICU patients (median, 0.143 vs. 0.000; p=0.002). They also had a greater number of high-risk pDDIs (categories D/X) (median, 1 [IQR, 0–1] vs. 0 [IQR, 0–1];

Table 1. Baseline demographic, clinical, and pDDI-related characteristics according to ICU type.

Variable	Medical ICU (n=154)	Surgical ICU (n=116)	p-value
Age, years	75.5 (65.3–82.0)	63.0 (46.0–77.0)	<0.001
Female, n (%)	70 (45.5)	42 (36.2)	0.127
APACHE II score	17 (13–21)	14 (9–17)	<0.001
Vasopressor use, n (%)	34 (22.1)	14 (12.1)	0.033
Mortality, n (%)	38 (24.7)	11 (9.5)	0.001
Total number of medications	9.5 (6–12)	10 (7–13)	0.444
Total number of unique pDDIs	5 (2–9)	5 (2–10)	0.957
High-risk pDDI ratio	0.143 (0–0.283)	0.000 (0–0.188)	0.002
High-risk pDDIs (D/X), median (IQR)	1 (0–1)	0 (0–1)	0.048
Patients with ≥1 high-risk pDDI, n (%)	90 (58.4)	50 (43.1)	0.013

Data are presented as median (interquartile range) or n (%).
ICU, intensive care unit; pDDI, potential drug–drug interaction; APACHE II, Acute Physiology and Chronic Health Evaluation II.

p=0.048), and a higher proportion of patients with at least one high-risk pDDI (58.4% vs. 43.1%; p=0.013).

Comparison of survivors and non-survivors

The demographic, clinical, and pDDI-related characteristics of survivors and non-survivors are presented in Table 2. Non-survivors were significantly older than survivors (median age, 77.0 vs. 70.0 years; $p=0.015$) and had higher APACHE II scores (median, 19.5 vs. 14.0; $p<0.001$). They also received a greater number of medications (median, 12 vs. 9; p<0.001), had a higher cumulative number of unique pDDIs (median, 6.5 vs. 5.0; p=0.027), a greater number of high-risk pDDIs (categories D/X) (median, 1 [IQR, 0–2] vs. 0 [IQR, 0–1]; p=0.021), and required vasopressor therapy more frequently (38.8% vs. 13.1%; p<0.001). However, no significant differences were observed between the groups in the high-risk pDDI ratio, the proportion of patients with at least one high-risk pDDI (61.2% vs. 49.8%; p=0.147), or sex (all p>0.05).

Multivariable analysis for in-hospital mortality

To evaluate the independent associations of medication burden and cumulative pDDI burden with in-hospital mortality, three multivariable logistic regression models were constructed (Table 3).

In Model 1, APACHE II score (OR, 1.094; 95% CI, 1.039–1.152; $p=0.001$), vasopressor use (OR, 2.211; 95% CI, 1.028–4.756; $p=0.042$), and the total number of medications (OR, 1.249; 95% CI, 1.124–1.387; $p<0.001$) were independently associated with in-hospital mortality.

In Model 2, APACHE II score (OR, 1.114; 95% CI, 1.059–1.172; $p<0.001$), vasopressor use (OR, 2.963; 95% CI, 1.407–6.241; $p=0.004$), and the cumulative number of unique pDDIs (OR, 1.082; 95% CI, 1.012–1.156; $p=0.021$) were independently associated with in-hospital mortality.

In Model 3, after simultaneous adjustment for the total number of medications and the cumulative number of unique pDDIs, only APACHE II score (OR, 1.087; 95% CI, 1.031–1.146; $p=0.002$) and the total number of medications (OR, 1.337; 95% CI, 1.151–1.554; $p<0.001$) remained independently associated with in-hospital mortality. The association between the cumulative number of unique pDDIs and in-hospital mortality was no longer statistically significant (OR, 0.938; 95% CI, 0.850–1.034; $p=0.199$).

Multivariable analysis for hospital length of stay

Three multivariable linear regression models were constructed to evaluate factors associated with hospital length of stay (Table 4).

In Model 1, higher APACHE II score (B = 0.873, 95% CI: 0.435–1.311; $p<0.001$) and the total number

Table 2. Comparison of demographic, clinical, and pDDI-related characteristics between survivors and non-survivors.

Variable	Survivors (n=221)	Non-survivors (n=49)	p-value
Age, years	70 (55–81)	77 (65.3–83.5)	0.015
Female, n (%)	91 (41.2)	21 (42.9)	0.829
APACHE II score	14 (10–18)	19.5 (16–24.8)	<0.001
Vasopressor use, n (%)	29 (13.1)	19 (38.8)	<0.001
Total number of medications	9 (6–11.3)	12 (10–14)	<0.001
Total number of unique pDDIs	5 (2–9)	6.5 (3.3–10)	0.027
High-risk pDDI ratio	0.083 (0–0.20)	0.183 (0–0.257)	0.090
High-risk pDDIs (D/X), median (IQR)	0 (0–1)	1 (0–2)	0.021
Patients with ≥1 high-risk pDDI, n (%)	110 (49.8)	30 (61.2)	0.147

Data are presented as median (interquartile range) for continuous variables and *n* (%) for categorical variables. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the Pearson χ^2 test or Fisher's exact test, as appropriate.
APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; pDDI, potential drug–drug interaction.

Table 3. Multivariable logistic regression analyses for predictors of in-hospital mortality.

Variable	Model 1 OR (95% CI)	p	Model 2 OR (95% CI)	p	Model 3 OR (95% CI)	p
Age	1.015 (0.993–1.037)	0.181	1.011 (0.990–1.032)	0.321	1.018 (0.995–1.041)	0.120
APACHE II score	1.094 (1.039–1.152)	0.001	1.114 (1.059–1.172)	<0.001	1.087 (1.031–1.146)	0.002
Vasopressor use	2.211 (1.028–4.756)	0.042	2.963 (1.407–6.241)	0.004	2.071 (0.961–4.465)	0.063
Total number of medications	1.249 (1.124–1.387)	<0.001	–	–	1.337 (1.151–1.554)	<0.001
Total number of unique pDDIs	–	–	1.082 (1.012–1.156)	0.021	0.938 (0.850–1.034)	0.199

Model fit: Model 1: −2 Log Likelihood = 198.669; Cox & Snell R^2 = 0.191; Nagelkerke R^2 = 0.311; Omnibus test, $p < 0.001$. Model 2: −2 Log Likelihood = 212.906; Cox & Snell R^2 = 0.147; Nagelkerke R^2 = 0.240; Omnibus test, $p < 0.001$. Model 3: −2 Log Likelihood = 196.997; Cox & Snell R^2 = 0.196; Nagelkerke R^2 = 0.319; Omnibus test, $p < 0.001$.
All multivariable regression models were fitted using the Enter method
Collinearity assessment: Multicollinearity was assessed using variance inflation factor (VIF) values. VIF values ranged from 1.13 to 2.51, indicating no evidence of problematic multicollinearity.
OR, odds ratio; CI, confidence interval; pDDI, potential drug–drug interaction; APACHE II, Acute Physiology and Chronic Health Evaluation II.

of medications (B = 1.623, 95% CI: 0.851–2.395; $p<0.001$) were independently associated with longer hospital length of stay.

In Model 2, higher APACHE II score (B = 1.080, 95% CI: 0.641–1.519; $p<0.001$) and vasopressor use (B = 9.694, 95% CI: 2.099–17.290; $p=0.013$) remained independently associated with hospital length of stay, whereas the cumulative number of unique pDDIs was not significantly associated with the outcome (B = 0.365, 95% CI: −0.226 to 0.956; $p=0.225$).

In Model 3, after simultaneous adjustment for the total number of medications and the cumulative number of unique pDDIs, higher APACHE II score (B = 0.740, 95% CI: 0.297–1.184; $p=0.001$) and the total number of medications (B = 2.755, 95% CI: 1.628–3.882; $p<0.001$) remained independently associated with longer hospital length of stay. The cumulative number of unique pDDIs was inversely associated with hospital length of stay (B = −1.145, 95% CI: −1.984 to −0.306; $p=0.008$), whereas vasopressor use was not independently associated with the outcome.

Multivariable analysis for ICU length of stay

Three multivariable linear regression models were constructed to evaluate factors associated with ICU length of stay (Table 5).

In Model 1, higher APACHE II score (B = 0.695, 95% CI: 0.388–1.001; $p<0.001$) and the total number of medications (B = 0.842, 95% CI: 0.301–1.382; $p=0.002$) were independently associated with longer ICU length of stay.

Table 4. Multivariable linear regression analyses for predictors of hospital length of stay.

Variable	Model 1 B (95% CI)	p	Model 2 B (95% CI)	p	Model 3 B (95% CI)	p
APACHE II score	0.873 (0.435 to 1.311)	<0.001	1.080 (0.641 to 1.519)	<0.001	0.740 (0.297 to 1.184)	0.001
Vasopressor use	6.225 (−1.357 to 13.807)	0.107	9.694 (2.099 to 17.290)	0.013	4.813 (−2.753 to 12.379)	0.211
Total number of medications	1.623 (0.851 to 2.395)	<0.001	–	–	2.755 (1.628 to 3.882)	<0.001
Total number of unique pDDIs	–	–	0.365 (−0.226 to 0.956)	0.225	−1.145 (−1.984 to −0.306)	0.008

Model fit: Model 1: R^2 = 0.176, adjusted R^2 = 0.167. Model 2: R^2 = 0.128, adjusted R^2 = 0.118. Model 3: R^2 = 0.198, adjusted R^2 = 0.186.
All multivariable regression models were fitted using the Enter method
Collinearity assessment: Multicollinearity was assessed using variance inflation factor (VIF) values. VIF values ranged from 1.13 to 2.51, indicating no evidence of problematic multicollinearity.
B, unstandardized regression coefficient; CI, confidence interval; pDDI, potential drug–drug interaction; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table 5. Multivariable linear regression analyses for predictors of ICU length of stay.

Variable	Model 1 B (95% CI)	p	Model 2 B (95% CI)	p	Model 3 B (95% CI)	p
APACHE II score	0.695 (0.388 to 1.001)	<0.001	0.807 (0.504 to 1.111)	<0.001	0.539 (0.236 to 0.842)	0.001
Vasopressor use	1.417 (−3.894 to 6.728)	0.600	3.608 (−1.648 to 8.865)	0.178	−0.248 (−5.414 to 4.918)	0.925
Total number of medications	0.842 (0.301 to 1.382)	0.002	–	–	2.177 (1.407 to 2.946)	<0.001
Total number of unique pDDIs	–	–	−0.157 (−0.566 to 0.252)	0.449	−1.350 (−1.923 to −0.777)	<0.001

Model fit: Model 1: R^2 = 0.141, adjusted R^2 = 0.131. Model 2: R^2 = 0.112, adjusted R^2 = 0.102. Model 3: R^2 = 0.205, adjusted R^2 = 0.194.
All multivariable regression models were fitted using the Enter method
Collinearity assessment: Multicollinearity was assessed using variance inflation factor (VIF) values. VIF values ranged from 1.13 to 2.51, indicating no evidence of problematic multicollinearity.
B, unstandardized regression coefficient; CI, confidence interval; pDDI, potential drug–drug interaction; APACHE II, Acute Physiology and Chronic Health Evaluation II.

In Model 2, higher APACHE II score was independently associated with ICU length of stay (B = 0.807, 95% CI: 0.504–1.111; $p<0.001$), whereas the cumulative number of unique pDDIs was not significantly associated with the outcome (B = −0.157, 95% CI: −0.566 to 0.252; $p=0.449$).

In Model 3, after simultaneous adjustment for the total number of medications and the cumulative number of unique pDDIs, higher APACHE II score (B = 0.539, 95% CI: 0.236–0.842; $p=0.001$) and the total number of medications (B = 2.177, 95% CI: 1.407–2.946; $p<0.001$) remained independently associated with longer ICU length of stay. The cumulative number of unique pDDIs was inversely associated with ICU length of stay (B = −1.350, 95% CI: −1.923 to −0.777; $p<0.001$).

Discussion

The present study evaluated the associations of potential drug–drug interactions (pDDIs) and medication burden with clinical outcomes in a mixed medical–surgical ICU population. Although the cumulative number of unique pDDIs was associated with in-hospital mortality in the model in which it was evaluated separately, this association was no longer significant after adjustment for the total number of medications. In contrast, the total number of medications remained independently associated with both in-hospital mortality and length of stay. In addition, patients admitted to the medical ICU had greater illness severity, a higher proportion of high-risk pDDIs, and higher in-hospital mortality than those admitted to the surgical ICU.

Polypharmacy and pDDIs are intrinsically linked in critically ill patients, as the likelihood of potential drug–drug interactions increases with the number of prescribed medications. Consistent with this relationship, previous ICU studies have identified the number of prescribed medications as one of the strongest predictors of pDDI occurrence (1-4,6,7). More recent studies have further shown that a higher medication burden is associated not only with an increased frequency of pDDIs but also with greater

illness severity and a higher risk of mortality (8,9). In agreement with these findings, both the total number of medications and the cumulative number of unique pDDIs were independently associated with in-hospital mortality when evaluated in separate multivariable models in our cohort. However, after simultaneous adjustment for both variables, only the total number of medications remained independently associated with mortality. These findings suggest that the observed association between pDDIs and mortality is largely explained by overall medication burden and that pDDIs should therefore be interpreted in the context of medication burden rather than in isolation.

Medical ICU patients in our study were older, had higher APACHE II scores, and experienced higher in-hospital mortality than surgical ICU patients. Similar findings have been reported in previous studies, in which advanced age and greater illness severity were consistently associated with increased mortality (3,10,11). In addition, although the total number of medications and the cumulative number of unique pDDIs were comparable between the two groups, the proportion of high-risk pDDIs was significantly higher among medical ICU patients. This difference is likely to reflect differences in prescribing patterns rather than medication quantity. Patients admitted to medical ICUs often require more complex pharmacological regimens, including cardiovascular, antithrombotic, corticosteroid, and anti-infective therapies, which are more likely to result in clinically significant drug–drug interactions (1,2,6). The differences observed between medical and surgical ICUs should be interpreted cautiously, as they are more likely to reflect differences in patient characteristics and illness severity than an independent effect of ICU type.

A key finding of the present study was that the cumulative number of unique pDDIs was independently associated with in-hospital mortality in the multivariable model that did not include the total number of medications. However, this association was no longer statistically significant after adjustment for the total number of medications. This finding is biologically plausible because the occurrence of potential drug–drug interactions is largely driven by the number of concurrently prescribed medications, a relationship that has been consistently demonstrated in previous ICU studies (1-4,6). Therefore, medication burden and pDDI burden should be considered closely related measures of pharmacotherapy complexity rather than entirely independent constructs. These findings highlight the importance of accounting for overall medication burden when evaluating the independent association between pDDIs and clinical outcomes in observational studies. From a clinical perspective, strategies aimed at minimizing clinically relevant drug–drug interactions should focus not only on identifying potentially hazardous drug combinations but also on optimizing overall medication burden. Consistent with previous ICU studies, APACHE II score remained independently associated with both mortality and length of stay, underscoring the dominant influence of illness severity on clinical outcomes (1,5,11). Similarly, vasopressor use remained independently associated with in-hospital mortality, consistent with its established role as a marker of hemodynamic instability and greater illness severity (5,11).

Medication burden remained independently associated with both hospital and ICU length of stay in multivariable models adjusted for APACHE II score and vasopressor use. This finding is consistent with previous studies showing that patients receiving a greater number of medications tend to have more complex clinical conditions and longer hospital and ICU stays (1,2,6). In contrast, when the total number of medications and the cumulative number of unique pDDIs were simultaneously included in the same regression model, the association between the cumulative number of unique pDDIs and both hospital and ICU length of stay became inverse. This finding should not be interpreted as evidence of a protective effect of pDDIs. One possible explanation is that patients with greater illness severity receive more medications and consequently accumulate a higher number of potential drug–drug interactions. At the same time, these patients are more likely to

experience early in-hospital death, thereby shortening their observed hospital and ICU length of stay. Consequently, the inverse association observed for the cumulative number of unique pDDIs in the fully adjusted model should be interpreted with caution and in the context of overall medication burden and illness severity. Taken together, these findings suggest that overall medication burden should be considered when interpreting the relationship between pDDIs and clinical outcomes and may represent a more clinically meaningful target for medication optimization than the number of potential drug–drug interactions alone.

The present study has several strengths. First, it included a relatively large cohort of critically ill patients from both medical and surgical ICUs, providing a comprehensive evaluation of pDDIs in a real-world intensive care setting. Second, unlike many previous studies, separate and combined multivariable models were constructed to distinguish the effects of medication burden from those of cumulative pDDI burden. This approach enabled a more rigorous evaluation of the independent associations of these two closely related variables with clinical outcomes. Finally, multiple clinically relevant outcomes, including in-hospital mortality, hospital length of stay, and ICU length of stay, were evaluated, allowing a more comprehensive assessment of the clinical implications of pDDIs and medication burden.

This study has several limitations. First, its retrospective, single-center design may limit the generalizability of the findings. Second, pDDIs were identified using the Lexicomp® database and therefore represent potential rather than clinically confirmed drug–drug interactions. In addition, the cumulative number of unique pDDIs reflects the number of distinct interaction pairs identified during the ICU stay rather than the cumulative duration of exposure to those interactions. Third, although the multivariable analyses adjusted for important clinical confounders, residual confounding cannot be excluded because of the observational nature of the study. Fourth, the study did not evaluate the actual occurrence or clinical severity of adverse drug events attributable to individual pDDIs. Finally, medication burden and cumulative pDDI burden are intrinsically related variables, and although separate and combined multivariable models were used, their complex interrelationship cannot be fully disentangled in an observational study. Prospective multicenter studies incorporating clinically confirmed drug-related adverse events are warranted to further clarify these relationships.

In conclusion, patients admitted to the medical ICU had a higher proportion of high-risk pDDIs and higher in-hospital mortality than those admitted to the surgical ICU. Both medication burden and the cumulative number of unique pDDIs were independently associated with in-hospital mortality when evaluated in separate multivariable models. However, after simultaneous adjustment, only medication burden remained independently associated with mortality, hospital length of stay, and ICU length of stay. These findings indicate that the association between pDDIs and clinical outcomes should be interpreted in the context of overall medication burden rather than in isolation. Future prospective multicenter studies incorporating clinically confirmed adverse drug events are warranted to further clarify the independent clinical impact of pDDIs in critically ill patients and to determine whether reducing medication burden can improve medication safety and clinical outcomes.

Ethical approval

This study has been approved by the Ethics Committee of Aksaray University Faculty of Health Sciences (approval date: March 5, 2026, number: 2026/78). The requirement for informed consent was waived because of the retrospective study design.

Author contribution

Study conception and design: AF, SBK; data collection: AF, SBK; analysis and interpretation of results: AF, SBK; draft manuscript preparation: AF, SBK. Both

authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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CASE REPORT

CytoSorb hemoadsorption in propafenone poisoning: a case report

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ABSTRACT

Background: Propafenone overdose is a rare but potentially fatal condition due to its potent sodium channel-blocking and cardiodepressant effects. Conventional extracorporeal elimination methods are typically ineffective owing to the drug's high protein-binding affinity and large volume of distribution. Hemoadsorption using the CytoSorb® device, although primarily developed for sepsis, may offer a novel therapeutic option in such intoxications.

Case Presentation: We describe a 38-year-old turkish female with a history of panic disorder and paroxysmal atrial fibrillation who presented to the emergency department after a suicide attempt involving the ingestion of an estimated 40 tablets of 150 mg propafenone. She exhibited generalized tonic-clonic seizures, severe metabolic acidosis, hypotension (BP 70/50 mmHg), bradycardia (HR 55 bpm), and QRS prolongation (>150 ms). Despite high-dose intravenous sodium bicarbonate, benzodiazepines, and vasopressor support, the patient's hemodynamic instability persisted. After ICU admission and further deterioration, the patient was intubated, and PiCCO monitoring was initiated. As a last resort prior to ECMO initiation, CytoSorb® hemoadsorption therapy was commenced. Within one hour, her ECG normalized, vasopressors were rapidly weaned, and cardiac index improved significantly. She was extubated 21 hours later and discharged without sequelae.

Conclusions: This case highlights the potential use of CytoSorb® hemoadsorption as an adjunctive therapy in severe propafenone poisoning, particularly in patients exhibiting refractory cardiotoxicity. Hemoadsorption may contribute to rapid clinical recovery and could potentially avert the need for more invasive interventions such as ECMO. Further clinical data are needed to validate its efficacy in this context.

Keywords: cardiotoxicity, CytoSorb, drug overdose, hemoadsorption, propafenone

Introduction

Hemoadsorption therapies have emerged as novel extracorporeal strategies for the removal of inflammatory mediators, endogenous toxins, and certain drugs from the circulation. Initially developed for sepsis and systemic hyperinflammatory states, devices such as CytoSorb have demonstrated potential in an expanding range of clinical indications, including liver failure, rhabdomyolysis, cytokine release syndrome, and drug intoxications. Their mechanism of action relies on the non-selective adsorption of hydrophobic and medium-sized molecules, particularly those with high protein-binding affinity. Despite the growing use of hemoadsorption in critically ill patients, its application in cases of lipophilic antiarrhythmic drug overdose remains largely unexplored (1,2). Propafenone, a class 1C antiarrhythmic agent with potent sodium channel-blocking properties, is widely used in the treatment of supraventricular and ventricular arrhythmias. In overdose situations, it can cause life-threatening cardiotoxic effects, including conduction delays,

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ventricular arrhythmias, profound hypotension, seizures, and cardiac arrest. Due to its high protein-binding rate (>90%) and large volume of distribution, conventional extracorporeal elimination techniques such as hemodialysis or hemofiltration are typically ineffective. Although CytoSorb hemoadsorption has shown promise in the removal of certain lipophilic and protein-bound drugs, there are currently no published reports describing its use in propafenone intoxication (3-6). To our knowledge, this case represents the first documented clinical application of CytoSorb in the management of severe propafenone poisoning.

Case Presentation

A 38-year-old female with a known history of panic disorder and paroxysmal atrial fibrillation attempted suicide by ingesting approximately 40 tablets of her prescribed medication, propafenone 150 mg. She was brought to the emergency department after a generalized tonic-clonic seizure. Her initial vital signs were: blood pressure 70/50 mmHg, heart rate 55 bpm, oxygen saturation 98%, and Glasgow Coma Scale score of 11. Electrocardiography (ECG) revealed atrial fibrillation, a widened QRS complex (>150 ms), and signs of sodium channel blockade. Arterial blood gas analysis indicated severe metabolic acidosis (pH 7.09, pCO_2 28 mmHg, HCO_3^- 9.9 mmol/L, base excess −21, lactate 8.5 mmol/L). Due to the absence of a drug assay at the facility, serum propafenone levels could not be measured. The estimated time of ingestion was unknown.

Due to electrocardiographic evidence of sodium-channel blockade and two generalized tonic–clonic seizures in the emergency department, the patient—whose QRS duration initially exceeded 150 ms—received five intravenous boluses of sodium bicarbonate (6 ampoules each) until QRS narrowing was achieved. When the QRS remained above 120 ms, a continuous infusion of sodium bicarbonate at 6 ampoules per hour was commenced. As seizures persisted, two intravenous doses of diazepam were administered. Despite ongoing bicarbonate therapy, seizure activity remained refractory and hemodynamic instability continued. Continuous infusions of sodium bicarbonate (6 ampoules/h), midazolam (1 mg/h), and norepinephrine (0.15 mcg/kg/min) were initiated. Upon ICU admission, the patient developed frequent tonic-clonic seizures, bradycardia, and worsening hypotension. She was intubated, and levetiracetam (1000 mg loading dose) was administered. Vasopressor support was escalated to norepinephrine (0.6 μg/kg/min) and adrenaline (0.5 μg/kg/min). Hemodynamic monitoring via PiCCO was initiated through a thermistor-tipped femoral arterial catheter and a jugular central line. Baseline PiCCO values were: cardiac index 1.85 L/min/m^2, systemic vascular resistance index 3205 dyn·s·m^2/cm^5, global end-diastolic volume index 428 mL/m^2, and extravascular lung water index 13 mL/kg (Figure 1A and Figure 1B).

As the patient remained hypotensive and bradycardic despite maximal supportive care, venoarterial ECMO was considered. Before ECMO initiation, CytoSorb hemoadsorption therapy was started at a blood flow rate of 140 ml/min. No additional therapeutic interventions were made during this period. Within one hour, ECG normalized with resolution of QRS widening, and vasopressors were weaned. After four hours of hemoadsorption, repeat PiCCO values showed hemodynamic improvement: CI 2.59 L/min/m^2, SVRI 2024 dyn·s·m^2/cm^5, GEDI 391 mL/m^2, and ELWI 11 mL/kg (Figure 2A and Figure 2B).

The patient was extubated at the 21st hour following intubation. On follow-up echocardiography, the ejection fraction was 65%, with trace mitral regurgitation. Right ventricular function was preserved, and cardiac output was measured at 4.4 L/min. She was discharged without neurological or cardiovascular sequelae.

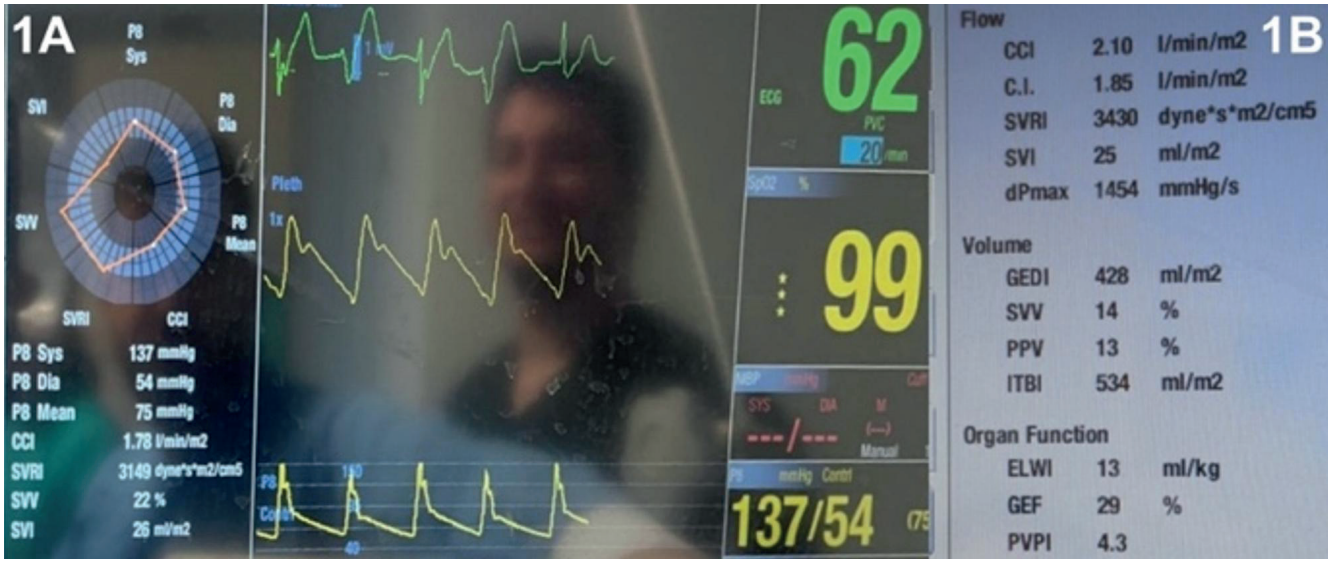

Figure 1. PiCCO hemodynamic monitoring before CytoSorb® hemoadsorption therapy: (A) hemodynamic monitoring display and (B) corresponding hemodynamic parameters.

Figure 2. PiCCO hemodynamic monitoring after CytoSorb® hemoadsorption therapy: (A) hemodynamic monitoring display and (B) corresponding hemodynamic parameters.

Discussion

The use of high-efficiency hemoadsorption filters such as CytoSorb may represent a reasonable approach for removing excess drugs from the circulation in cases of intoxication. However, the current literature on this topic remains limited, and it is still unclear which drugs can be effectively eliminated in overdose settings (1-5). This case was documented specifically to provide clinical insight and guidance for physicians facing similar challenges. In the emergency setting, where rapid stabilization is crucial and conventional detoxification methods offer limited benefit, hemoadsorption may provide an additional therapeutic option for selected patients.

CytoSorb can adsorb molecules ranging from 5 to 60 kDa, encompassing various substances including cytokines associated with sepsis (e.g., IL-6, IL-1β, TNF-α), certain medications (e.g., ticagrelor, rivaroxaban), bilirubin, myoglobin, and other medium-sized molecular toxins (6-8). In albumin-bound compounds, only the unbound fraction is available for adsorption. Large proteins (>60–70 kDa), such as albumin and immunoglobulin G (IgG), are not removed by the CytoSorb filter. Nonetheless, CytoSorb has demonstrated the ability to adsorb certain small, lipophilic molecules — such as ticagrelor and amlodipine — even when they are highly protein-bound.

For effective adsorption, substances must be small enough to enter the polymer beads and sufficiently hydrophobic to facilitate physicochemical interactions with the polymer matrix. The removal process is concentration-dependent, with greater efficiency at elevated plasma concentrations. Importantly, CytoSorb use does not result in substantial depletion of albumin, coagulation factors, or immunoglobulins (9). It does not activate the coagulation or complement systems and is typically associated with only a minimal and transient reduction in platelet count.

One of the most consistent effects of CytoSorb therapy in patients with septic or vasoplegic shock is improved hemodynamic stability, usually accompanied by reduced vasopressor requirements, as highlighted in a recent review (10). Although the optimal timing for initiating therapy remains debated, early initiation—ideally within the first 12 hours following diagnosis—is generally recommended.

The volume of distribution (VD) is a critical pharmacokinetic parameter influencing the effectiveness of extracorporeal drug removal. Agents with a low VD (<1 L/kg) are confined to the intravascular compartment and are more amenable to extracorporeal clearance. In contrast, drugs with a high VD (≥1 L/kg) distribute extensively into extravascular tissues and are less accessible for such techniques (10). While high protein binding (≥80%) can restrict tissue distribution and reduce VD, thereby potentially enhancing clearance through adsorption, it may simultaneously limit the availability of unbound drug required for effective removal.

In the absence of pharmacokinetic data obtained during CytoSorb treatment, precise dosing recommendations cannot be reliably established. Nonetheless, fundamental pharmacokinetic parameters such as molecular weight, hydrophobicity, volume of distribution, half-life, and protein binding provide useful insights into the likelihood of meaningful drug removal. Drugs prone to CytoSorb elimination typically show rapid clearance within the first 1–2 hours of therapy. This timeframe closely parallels the dramatic clinical response observed in our patient: electrocardiographic abnormalities improved within the first hour, and vasopressor demand decreased significantly. Although CytoSorb has been shown to remove various anti-infective agents from the bloodstream, its overall impact on most systemic pharmacokinetics appears minimal. Enhanced clearance has, however, been described for fluconazole, linezolid, and liposomal amphotericin B (11). In our case, the overdosed agent was propafenone—a small, lipophilic molecule (molecular weight 341.45 Da) characterized by high protein binding (>90–95%) and a large volume of distribution (1.9–3 L/kg). These properties theoretically limit the effectiveness of extracorporeal elimination via hemoadsorption. Nonetheless, CytoSorb has demonstrated partial efficacy in the removal of other highly protein-bound and lipophilic compounds, suggesting a potential role in the management of propafenone intoxication (12-14).

Based on our clinical observations, CytoSorb may have contributed to drug removal and to the rapid reversal of cardiotoxicity under specific conditions.

As evidence remains limited and no pharmacokinetic confirmation is available, the use of CytoSorb in propafenone poisoning should be considered on a case-by-case basis and reserved as a last-resort option in rapidly deteriorating patients when conventional supportive strategies fail.

Conclusion

With ongoing technological advancements, hemoadsorption therapies are increasingly supported by clinical evidence and are transitioning from being considered solely as rescue interventions to becoming adjunctive components of critical care, particularly in high-mortality conditions such as septic shock. As demonstrated in our patient, hemoadsorption with CytoSorb may be considered a last-resort option in severe propafenone intoxication, especially in cases of refractory cardiotoxicity where conventional measures fail and escalation to invasive treatments such as cardiac pacing or VA-ECMO is being contemplated. However, the effectiveness of drug removal depends on the pharmacokinetic characteristics of the agent and the clinical context. Therefore, decisions regarding the initiation of hemoadsorption should be individualized and, whenever possible, supported by therapeutic drug monitoring.

Ethical approval

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

Author contribution

Case conception and clinical management: DA, AOK, MPK; data collection and clinical documentation: DA, AOK, MPK, EA, VÖ; interpretation of clinical findings: EP, AOK, MPK; manuscript preparation: DA, EP, MPK, VÖ. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

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CASE REPORT

Carnitine palmitoyltransferase II deficiency: a case of post-infectious rhabdomyolysis and respiratory failure

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ABSTRACT

Carnitine palmitoyltransferase II (CPT-II) deficiency is an autosomal recessive inherited metabolic disorder and represents the most common genetic cause of recurrent rhabdomyolysis in adulthood. The clinical course is characterized by episodic attacks precipitated by intense physical exertion, infections, psychological stress, or other physical and emotional stressors. Although avoidance or early recognition of triggering factors plays a critical role in prognosis, many patients continue to experience recurrent episodes of rhabdomyolysis. Management primarily focuses on elimination of precipitating factors and meticulous correction of fluid and electrolyte imbalances. Prompt recognition of CPT-II deficiency and rapid identification and management of rhabdomyolysis triggers are essential for preventing life-threatening complications.

We report the clinical characteristics, therapeutic interventions, and outcome of a 31-year-old male patient with known CPT-II deficiency. The patient presented with dyspnea and generalized muscle weakness following an infectious episode. Laboratory evaluation revealed markedly elevated creatine kinase levels, and rhabdomyolysis secondary to CPT-II deficiency was diagnosed. The patient received supportive management, including intravenous fluid therapy for electrolyte stabilization, close monitoring in the intensive care unit, and treatment with triheptanoin. His symptoms improved gradually, and he was discharged in stable condition with recommendations emphasizing avoidance of known triggers and long-term disease management.

This report aims to underscore the importance of early diagnosis and timely therapeutic intervention in the management of CPT-II deficiency.

Keywords: CPT-II deficiency, rhabdomyolysis, respiratory failure, triheptanoin

Introduction

The CPT2 gene is inherited in an autosomal recessive manner. Although rare, carnitine palmitoyltransferase II (CPT-II) deficiency represents one of the most common genetic causes of rhabdomyolysis in adults (1) Approximately 300 cases have been reported in the literature; however, the true prevalence is likely underestimated (2) The enzymes CPT-I and CPT-II play pivotal roles in the transport of long-chain fatty acids into the mitochondria and, consequently, in the β-oxidation pathway. Long-chain fatty acid oxidation constitutes a major source of cellular energy production during periods of increased metabolic demand, such as prolonged or intense exercise, fasting, cold exposure, and psychological stress. Accordingly, CPT-II deficiency becomes clinically manifest under such stress conditions. In affected individuals, impaired translocation of acyl-carnitine across the mitochondrial membrane results in insufficient intramitochondrial acyl-CoA availability for β-oxidation, ultimately leading to cellular energy deficiency (3).

CPT-II deficiency is classified into three principal phenotypic forms. The neonatal and infantile forms

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present early in life, are associated with severe hypoketotic hypoglycemia and high mortality, and typically follow a critical clinical course. In contrast, the adult-onset myopathic form is generally milder and is characterized by recurrent episodes of myalgia, muscle weakness, and rhabdomyolysis triggered by prolonged exercise. The clinical spectrum of the adult form is heterogeneous; some individuals remain asymptomatic for extended periods, whereas others experience frequent and severe attacks (1,4).

Therapeutic strategies primarily focus on avoidance of precipitating factors, including fasting, strenuous exercise, and infections, as well as metabolic load reduction. Low-fat, high-carbohydrate diets are commonly recommended, and supplementation with medium-chain triglycerides (MCTs) has been reported to alleviate symptoms in certain cases (2,5) In recent years, triheptanoin—a synthetic odd-chain medium-chain triglyceride—has been approved as a promising therapeutic option for long-chain fatty acid oxidation disorders, including CPT-II deficiency. Nevertheless, long-term efficacy data remain limited (6).

Although CPT-II deficiency may present in childhood with variable organ involvement and biochemical abnormalities, the adult-onset form is most commonly characterized by exercise-induced rhabdomyolysis and myoglobinuria. The acyl-carnitine profile is widely used as a first-line diagnostic tool; however, in some late-onset cases, this profile may be normal, and definitive diagnosis may only be established through molecular genetic testing (7). Even during acute episodes, routine biochemical screening may yield normal results, thereby underscoring the importance of molecular genetic analysis. A case report published in 2024 highlighted that pathogenic CPT2 mutations may be identified despite normal biochemical screening, emphasizing the critical role of molecular testing in confirming the diagnosis (8).

These findings suggest that CPT-II deficiency should be considered in the differential diagnosis of patients presenting with recurrent rhabdomyolysis or unexplained respiratory failure, even in the presence of normal standard biochemical markers such as acyl-carnitine profiles or triglyceride levels. This consideration is particularly relevant for emergency and intensive care physicians, as reliance solely on routine metabolic screening may delay diagnosis and appropriate metabolic management (8).

From an anesthesiology perspective, perioperative complications have been reported in patients with CPT-II deficiency. Although a potential association between CPT-II deficiency and susceptibility to malignant hyperthermia has been proposed, evidence supporting the role of volatile anesthetic agents or succinylcholine in triggering malignant hyperthermia-like reactions remains limited (9). Propofol infusion has been discouraged by some experts due to concerns regarding the risk of propofol infusion syndrome (10). Furthermore, an experimental rat model of CPT-II deficiency demonstrated an association with bupivacaine-induced cardiotoxicity (11).

In this case report, we describe a 31-year-old male patient who presented to the emergency department with respiratory failure following an infectious episode. Rare metabolic disorders, including mitochondrial myopathies and CPT-II deficiency, may initially manifest as acute rhabdomyolysis and respiratory failure. This report aims to emphasize the importance of early recognition and timely therapeutic intervention in the management of CPT-II deficiency.

Case report

A 31-year-old male patient, with no history of smoking or alcohol consumption, measuring 185 cm in height and weighing 75 kg, had been previously evaluated for recurrent episodes of rhabdomyolysis and was diagnosed with CPT-II deficiency approximately five years earlier. Since the diagnosis, he has been regularly followed by specialists in endocrinology and metabolism, as well as a dietitian. He has been receiving triheptanoin therapy and adheres to a low-fat, high-carbohydrate diet while strictly avoiding prolonged fasting.

Three days after the onset of upper respiratory tract infection symptoms, the patient presented to the emergency department with acute worsening dyspnea and high-grade fever. On initial assessment, he was conscious, tachypneic, and hypoxemic. Laboratory investigations demonstrated a marked elevation in creatine kinase (CK) levels (increasing from 19,834 U/L to 50,254 U/L), a dramatic rise in liver enzymes (AST/ALT from 354/120 U/L to 1101/457 U/L), and elevated troponin I (cTnI) levels (from 5.7 ng/mL to 11.5 ng/mL). In contrast, blood urea nitrogen (BUN) and serum creatinine levels were within normal limits (Table 1). Venous blood gas (VBG) analysis revealed acidosis, hypercapnia, and hypoxemia (pH 7.29, pCO_2 59 mmHg, pO_2 20 mmHg) (Table 2).

The patient was admitted to the intensive care unit (ICU) by the critical care team. Empirical intravenous antibiotics (ceftriaxone and moxifloxacin) were initiated for the suspected underlying infection, along with fluid and electrolyte replacement and targeted metabolic management for rhabdomyolysis. Urine, blood, and respiratory tract cultures were obtained, and a respiratory PCR panel was sent. A chest radiograph was performed as part of the diagnostic evaluation. Although tachypnea improved, persistent hypoxemia continued. Due to poor tolerance of noninvasive mechanical ventilation and significant agitation in the setting of ongoing hypoxemia, elective endotracheal intubation was performed.

Given the underlying fatty acid oxidation disorder, propofol was avoided because of the potential risk of propofol infusion syndrome. Sedation was achieved with midazolam and fentanyl in a manner aimed at preserving hemodynamic stability and minimizing additional metabolic burden. Neuromuscular blockade was induced with rocuronium, followed

Table 1. Distribution of laboratory parameters throughout the clinical course.

Parameter	Value 1	Value 2	Value 3	Value 4	Value 5
White Blood Cell (WBC, ×10³/µL)	10.42	9.41	6.25		
Hemoglobin (Hb, g/dL)	16.9	16.8	14.3		
Hematocrit (HCT, %)	48.5	48.5	44.2		
Platelet (PLT, ×10³/µL)	212	186	178		
Neutrophil (NEU, ×10³/µL)	8.28	8.58	3.75		
Lymphocyte (LYM, ×10³/µL)	0.98	0.66	1.66		
Urea (mg/dL)	35	17	53	35	32
Creatinine (mg/dL)	0.96	1.26	2.5	0.99	0.82
Aspartate Aminotransferase (AST, U/L)	354	500	552	1101	962
Alanine Aminotransferase (ALT, U/L)	120	161	185	336	457
Creatine Kinase (CK, U/L)	19.834	27.539	28.234	50.254	32.593
Creatine Kinase-MB (CK-MB, U/L)	457	494	226	308	236
C-Reactive Protein (CRP, mg/L)	3.69	7.36			
Procalcitonin (ng/mL)	0.14	0.07			
Albumin (g/L)	45.2	44	31		
Potassium (K, mmol/L)	3.90	3.95	3.68	3.76	
Sodium (Na, mmol/L)	140	137	142	140	
Direct Bilirubin (mg/dL)	0.12	0.10	0.11	0.08	
Total Bilirubin (mg/dL)	0.50	0.46	0.48	0.37	
Ammonia (µmol/L)	33.4	53.6	48.6		
Troponin (ng/mL)			5.70	11.5	6

WBC: White Blood Cell, Hb: Hemoglobin, Hct: Hematocrit, PLT: Platelet, NEU: Neutrophil, LYM: Lymphocyte, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CK: Creatine kinase, CK-MB: Creatine Kinase-MB isoenzyme, CRP: C-reactive protein.

Table 2. Changes in venous blood gas parameters during the intensive care unit (ICU) stay.

	ph	PCO_2 (mmHg)	PO_2 (mmHg)	HCO_3 (mEq/L)	Laktat (mmol/L)	O_2 Sat (%)
1	7.29	57.4	20.3	22.5	0.4	28.2
2	7.25	64.9	18.8	21.5	1.7	31.4
3	7.39	39.0	41.0	23.4	2.1	80.4
4	7.39	52.6	22.8	29.4	1.5	84.8
5	7.35	59.3	43.0	28.4	1.6	80.7
6	7.44	39.0	51.0	26.6	1.7	90.5
7	7.35	56.0	55.0	27.0	1.3	75.0
8	7.38	51.0	37.0	27.0	0.9	69.5

by endotracheal intubation and initiation of invasive mechanical ventilation (IMV).

Early in the course of rhabdomyolysis management, aggressive intravenous isotonic crystalloid therapy was administered. Fluid therapy was titrated to achieve a target urine output of ≥1–2 mL/kg/hour. Serum CK levels, renal function parameters, and electrolytes were monitored serially. When clinically indicated, urine alkalinization was performed, with a target urine pH >6.5. Electrolyte abnormalities were corrected appropriately. On the following day, the patient was successfully extubated and transitioned to high-flow nasal oxygen (HFNO) therapy in conjunction with respiratory physiotherapy. Oxygen support was gradually tapered over the subsequent days, first to nasal cannula and ultimately to room air, with maintenance of stable oxygenation.

During clinical follow-up, progressive improvement in metabolic parameters was observed. CK, AST, ALT, and cTnI levels declined steadily, while ABG parameters and oxygen saturation normalized. Under multidisciplinary care, triheptanoin dosing and dietary management were meticulously maintained. The patient's clinical condition stabilized, and he was transferred from the ICU to the general ward in good overall condition.

Discussion

Currently, no disease-specific standardized intensive care protocol exists for CPT-II deficiency. However, in patients with fatty acid oxidation disorders, prevention of metabolic stress constitutes the cornerstone of management. Avoidance of fasting, provision of adequate carbohydrate supplementation, restriction of lipid load, and prevention of catabolism are essential components of care. In cases complicated by rhabdomyolysis, early and aggressive fluid resuscitation is fundamental to preserving renal function. Furthermore, avoidance of agents that may inhibit mitochondrial fatty acid oxidation—such as propofol—is recommended. A multidisciplinary approach plays a critical role in maintaining metabolic stability (2,10,12).

At present, there is no curative therapy for carnitine palmitoyltransferase II (CPT-II) deficiency, and existing treatment strategies are primarily directed toward symptom control and prevention of metabolic crises (12). The principal therapeutic objectives during acute rhabdomyolysis episodes include prevention of acute kidney injury, correction of life-threatening electrolyte disturbances, and cessation of ongoing muscle breakdown. The literature emphasizes that early, multidisciplinary management and intensive care support are potentially life-saving, particularly during severe metabolic crises (13). In a systematic review by Ivin et al., a substantial proportion of CPT-II–associated rhabdomyolysis cases required organ support, underscoring the severity of such episodes (5).

Early and aggressive intravenous crystalloid fluid resuscitation remains the cornerstone of rhabdomyolysis management. This strategy is critical

for correcting hypovolemia, preventing acute kidney injury, and enhancing renal clearance of myoglobin. Strict bed rest and carbohydrate supplementation have also been reported to reduce the severity of muscle injury during acute attacks in CPT-II deficiency. Patients should be strongly advised to avoid strenuous physical activity (12).

From a nutritional perspective, low-fat, high-carbohydrate diets and minimization of fasting periods contribute to metabolic stability. Prevention of hypoglycemia is particularly important, as it reduces the risk of arrhythmias and rhabdomyolysis (14). In recent years, medium-chain triglycerides such as triheptanoin have emerged as promising therapeutic alternatives for long-chain fatty acid oxidation disorders. Triheptanoin supports the tricarboxylic acid (TCA) cycle through the generation of acetyl-CoA and propionyl-CoA, thereby mitigating cellular energy deficits. Clinical reports suggest a reduction in both the frequency and severity of rhabdomyolysis episodes with triheptanoin therapy; however, long-term safety and efficacy data remain limited (6). By providing anaplerotic substrates to the TCA cycle, triheptanoin may enhance cellular energy production during metabolic stress. Nevertheless, its use in the intensive care setting should be individualized and closely monitored. Although long-term efficacy data in CPT-II deficiency remain limited, current evidence suggests a potential therapeutic benefit (15). In our case, triheptanoin-supported metabolic therapy was considered to have contributed to clinical recovery.

As in other metabolic myopathies, rhabdomyolysis represents the most common cause of hospital admission in patients with CPT-II deficiency. In most cases, episodes are triggered by identifiable precipitating factors (12) Although rhabdomyolysis and respiratory failure are well-recognized entities in critical care practice, the coexistence of infection-triggered rhabdomyolysis and hypercapnic respiratory failure in adult-onset CPT-II deficiency has been rarely addressed in the literature. Respiratory failure in CPT-II deficiency is infrequently reported and remains a noteworthy clinical presentation (16).

Infection is a well-established trigger of metabolic decompensation and rhabdomyolysis in patients with CPT-II deficiency. Recent case reports and reviews emphasize that early identification of the infectious agent and timely initiation of appropriate antimicrobial therapy are essential to limit metabolic stress and prevent severe organ dysfunction (14-16). Accordingly, whenever feasible, identification of the causative microorganism and administration of targeted antimicrobial therapy may represent a critical component of management beyond empirical treatment alone.

At presentation, the patient exhibited fever and respiratory distress. Initial laboratory parameters did not demonstrate marked abnormalities beyond mild elevations consistent with a systemic inflammatory response. Imaging studies did not reveal findings suggestive of pneumonia. Despite the absence of definitive bacterial infection, empirical intravenous antibiotic therapy (ceftriaxone and moxifloxacin) was initiated due to the patient's severe metabolic stress, the risk of secondary bacterial infection, and the anticipated need for intensive care interventions. Blood and sputum cultures yielded no growth. The respiratory viral panel was positive for respiratory syncytial virus (RSV). With clinical improvement, inflammatory parameters regressed. Viral infections, particularly respiratory viruses such as RSV, constitute significant metabolic stressors capable of precipitating decompensation and rhabdomyolysis in patients with CPT-II deficiency.

In this case, infection was identified as the precipitating factor. CK levels exceeding 50,000 U/L and marked elevations in AST and ALT were interpreted as indicators of severe muscle injury. Troponin I levels increased up to 11.5 ng/mL. However, the patient did not exhibit typical anginal symptoms, dynamic ST-segment changes, or hemodynamic instability suggestive of acute coronary syndrome. Electrocardiography revealed no ischemic abnormalities, and transthoracic

echocardiography demonstrated preserved left ventricular systolic function without regional wall motion abnormalities. The troponin elevation was therefore attributed to secondary myocardial injury related to systemic inflammatory response and metabolic stress associated with rhabdomyolysis. Troponin levels declined in parallel with clinical improvement.

Arterial blood gas analysis and clinical progression were consistent with severe respiratory failure. The pathophysiology of respiratory failure in this case was likely multifactorial and could not be explained solely by infection-related hypoxemia. In CPT-II deficiency, impaired long-chain fatty acid oxidation leads to pronounced energy deficiency in skeletal and respiratory muscles during periods of increased metabolic demand. This may result in early diaphragmatic fatigue and reduced ventilatory reserve. Moreover, the systemic inflammatory response accompanying acute rhabdomyolysis may further impair respiratory muscle performance through cytokine-mediated dysfunction and mitochondrial impairment. Infection likely amplified metabolic stress and energy depletion, thereby facilitating the development of hypercapnic respiratory failure.

Reviews examining the association between rhabdomyolysis and multiorgan dysfunction suggest that the metabolic burden of extensive muscle breakdown may affect not only renal function but also other organ systems, including the respiratory system (17-19). In our patient, the observed hypercapnia and requirement for mechanical ventilation can be attributed to the combined effects of respiratory muscle fatigue, cellular energy deficiency, and infection-triggered systemic inflammation.

Systematic reviews indicate that patients with CPT-II–associated rhabdomyolysis frequently require intensive care support, further highlighting the importance of early recognition and prompt management (5). In the present case, however, a multidisciplinary approach, early intensive care intervention, rapid diagnostic assessment, and timely initiation of metabolic therapy enabled successful extubation and clinical stabilization. These findings underscore the critical role of early intervention and close monitoring in the management of severe metabolic crises associated with CPT-II deficiency.

Conclusion

In patients with CPT-II deficiency, infections may precipitate severe rhabdomyolysis and respiratory failure. In cases of abrupt clinical deterioration associated with infection, early intensive care support and prompt initiation of targeted metabolic therapy may be life-saving. Fatty acid oxidation disorders should be considered in the differential diagnosis of unexplained rhabdomyolysis accompanied by hypercapnic respiratory failure.

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Ethical approval

Written informed consent for publication was obtained from the patient.

Author contribution

Study conception and design: HY, GK, MÇ; data collection: HY, VY, YÖ; analysis and interpretation of results: HY, GK, MÇ; draft manuscript preparation: HY; critical review and supervision: GK, MÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE SERIES

Use of bivalirudin in patients during veno-venous extracorporeal membrane oxygenation: a case series

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ABSTRACT

Objective: This study aimed to evaluate the use of bivalirudin as an alternative to conventional anticoagulant therapy with heparin in patients requiring venovenous extracorporeal membrane oxygenation (V-V ECMO) support for Acute Respiratory Distress Syndrome (ARDS), with a focus on dose titration, therapeutic range monitoring, complications, and clinical outcomes.

Materials and Methods: This retrospective case series included six patients who received V-V ECMO support and systemic anticoagulation with bivalirudin between August 2021 and April 2022 at Sakarya University Training and Research Hospital due to a diagnosis of ARDS. Activated clotting time (ACT), activated partial thromboplastin time (aPTT), daily bivalirudin infusion doses, ECMO-related complications, and clinical outcomes were retrospectively analyzed.

Results: Bivalirudin infusion doses ranged between 0.01 and 0.2 mg/kg/h across all patients. ACT values were maintained within the target range in all cases, while aPTT values remained below target in four patients. Hemorrhagic complications were observed in two patients, while thrombotic events occurred in another two. In one patient, bivalirudin infusion was discontinued due to the development of acute kidney injury. Of the six patients, two were discharged, while four died during follow-up.

Conclusion: Bivalirudin appears to be a safe and effective alternative anticoagulant agent for patients undergoing V-V ECMO. However, individualized and meticulous anticoagulation monitoring is essential, particularly in the context of renal dysfunction, the strengths and limitations of aPTT and ACT monitoring, and the delicate balance between hemorrhagic and thrombotic risks.

Keywords: Bivalirudin, ECMO, COVID-19, anticoagulation, aPTT, ACT, ARDS

Introduction

Today, veno-venous extracorporeal membrane oxygenation (V-V ECMO) is a treatment modality used in the management of Acute Respiratory Distress Syndrome (ARDS) due to many different causes and may be required in cases that do not respond to conventional mechanical ventilation.

During veno-venous extracorporeal membrane oxygenation (V-V ECMO), anticoagulation is necessary to reduce the risk of thrombosis and maintain ECMO circuit function. Since this treatment also carries a risk of bleeding, it requires careful management. In ARDS cases associated with COVID-19, achieving this balance is difficult because of the existing hypercoagulable state, which significantly increases the risk of both venous and arterial thromboembolic complications (1-3). Unfractionated heparin is generally used as the anticoagulant during ECMO because of its rapid onset of action, widespread availability, and reversibility with protamine (4,5). To date, unfractionated heparin (UFH) has been identified as the primary antithrombotic agent recommended in Extracorporeal Life Support

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Organization (ELSO) guidelines (2). However, heparin has inherent limitations, including susceptibility to persistent fluctuations in dose responsiveness and heparin-induced thrombocytopenia (HIT) (6). These potential problems associated with traditionally used unfractionated heparin (UFH), together with the goal of achieving better patient outcomes, have led to the need for alternative anticoagulation strategies in ECMO.

As an alternative anticoagulant in ECMO, bivalirudin, a direct thrombin inhibitor (DTI), has begun to be preferred because it provides predictable pharmacokinetics due to its organ-independent clearance and allows a balance between thrombosis and hemorrhage (7,8).

In this case series, we aimed to present the follow-up and treatment process of our patients who received veno-venous ECMO and were anticoagulated with bivalirudin.

Materials and methods

This retrospective case series included patients who received veno-venous ECMO support due to COVID-19-related ARDS at Sakarya University Training and Research Hospital between August 2021 and April 2022. Approval for the study was obtained from the Sakarya University Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (No: 71522473-050.01.04-136950-156).

The patients' age, sex, day of ECMO initiation, and laboratory values were recorded. During ECMO, hourly activated clotting time (ACT), activated partial thromboplastin time (aPTT) every 4 hours, and hourly bivalirudin dose values were recorded. Complications occurring during ECMO and intensive care unit and hospital outcomes were also recorded.

All patients received a bolus dose of heparin during ECMO cannulation, followed by initiation of a bivalirudin infusion. During ECMO, bivalirudin was initiated at 2.5 mcg/kg/min as recommended in the ECMO bivalirudin dosing protocol proposed by Netley et al.(9). According to the same protocol, the target aPTT was 50–70 seconds; however, because ACT values were considered more suitable for our hospital practice, we primarily targeted ACT values. Although there are differing opinions regarding the target ACT range, we determined the ACT target (for the i-STAT analyzer) to be between 160 and 200 seconds (10).

Complications developing during ECMO, daily mean bivalirudin dose, aPTT, and ACT levels were demonstrated graphically for each case.

Results

The data of six patients who received veno-venous ECMO support for ARDS and were anticoagulated with bivalirudin between August 2021 and April 2022 were included in the study. All cases were considered suitable for ECMO according to the recommendations in the ELSO guidelines (11).

Case 1

The first case was a 46-year-old male patient. The clinical events timeline of the case is shown in Figure 1. The daily mean bivalirudin dose administered during ECMO ranged between 0.015 mg/kg/h and 0.15 mg/kg/h. ACT was maintained within the target range, with a mean value of 174 seconds. The mean aPTT was 49 seconds, which was below the target range. On day 9 of ECMO, while ACT and aPTT values were within the target ranges, the patient developed gastrointestinal bleeding. Following the development of acute kidney injury on day 17, the bivalirudin requirement necessary to maintain target ACT and aPTT values decreased to 0.015 mg/kg/h. During follow-up, the patient developed a need for renal replacement therapy and died on day 19 of ECMO due to multiorgan failure.

Case 2

The second case was a 31-year-old female patient. The clinical events timeline of the case is shown in Figure 2. The mean bivalirudin dose administered during ECMO varied between 0.027 mg/kg/h and 0.36 mg/kg/h. ACT was maintained within the target range, with a mean value of 164 seconds. The mean aPTT was 37 seconds, which was below the target range. No bleeding or thrombosis was detected. The patient died on day 16 of ECMO due to worsening hypoxemia.

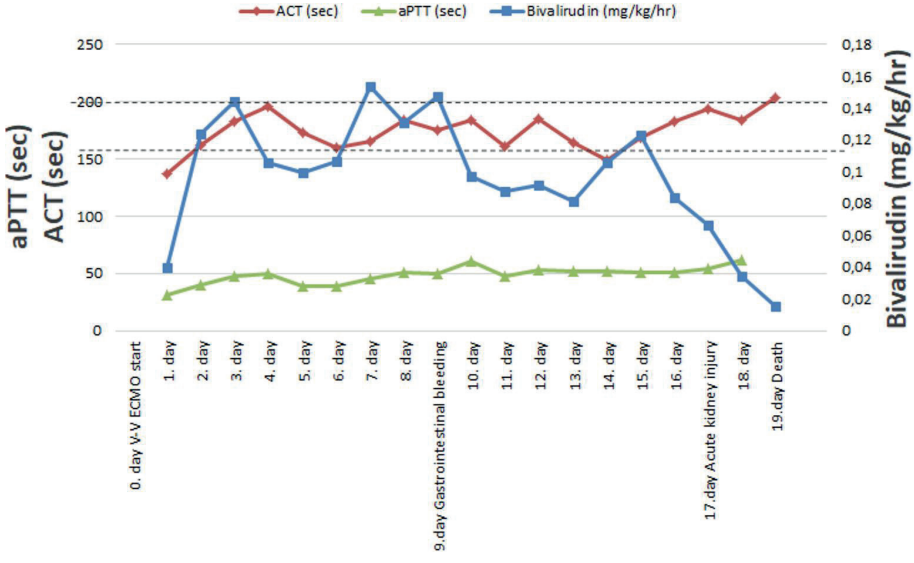

Figure 1. Case 1 clinical events timeline.

ACT target range: 160-200 sec, aPTT target range: 50-70sec, ACT (mean): 174sec, aPTT(mean):49sec.

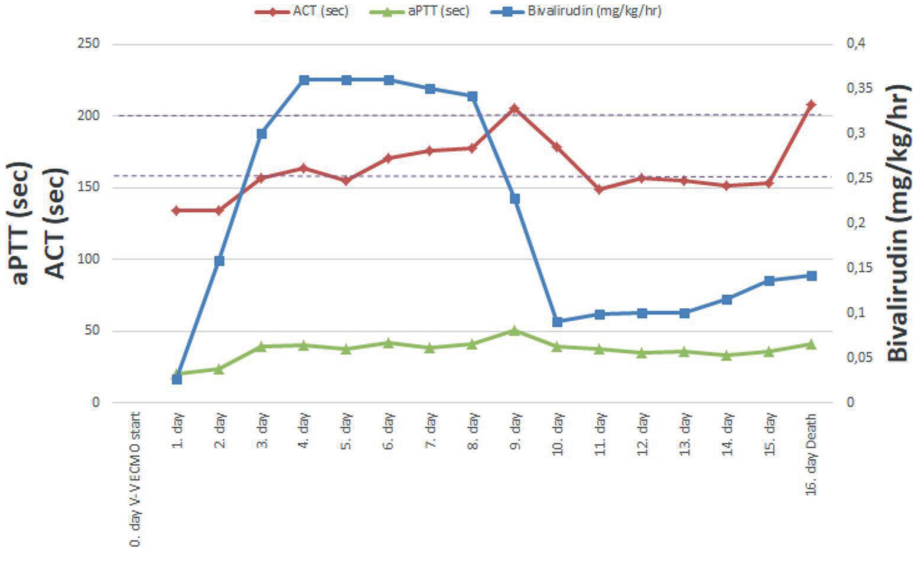

Figure 2. Case 2 clinical events timeline.

ACT target range:160-200 sec, aPTT target range:50-70sec, ACT (mean): 164sec, aPTT(mean):37sec.

Case 3

The third case was a 42-year-old male patient. The clinical events timeline of the case is shown in Figure 3. During the first 11 days of ECMO, the daily mean bivalirudin dose was 0.015 mg/kg/h, and ACT remained within the target range. On day 12, following the development of acute kidney injury (KDIGO stage 2, GFR 30–50 mL/min/1.73 m^2), the bivalirudin dose was reduced to as low as 0.0001 mg/kg/h. On day 18, the bivalirudin infusion was discontinued because ACT values were at the upper limit of the target range. After ACT values returned to the target range, a percutaneous tracheostomy was performed on day 21. Subsequently, acute kidney injury progressed, and the patient required renal replacement therapy. Since ACT and aPTT values continued to remain above the target range, bivalirudin infusion was not restarted. The patient developed bleeding around the tracheostomy site on day 23, gastrointestinal bleeding on day 25, and catheter-site bleeding on day 28. Disseminated intravascular coagulation (DIC) developed on day 30. The patient developed pulmonary hemorrhage on day 36 and died on day 37.

Case 4

The fourth case was a 33-year-old female patient. The clinical events timeline of the case is shown in Figure 4. The mean bivalirudin dose administered during ECMO varied between 0.025 mg/kg/h and 0.099 mg/kg/h. Throughout ECMO, ACT was maintained within the target range, with a mean value of 166 seconds. The mean aPTT was 44 seconds, which was below the target range. However, despite ACT and aPTT values being within the target ranges, the patient developed a massive pulmonary embolism on day 14 and died.

Case 5

The fifth case was a 50-year-old male patient. The clinical events timeline of the case is shown in Figure 5. The daily mean bivalirudin dose administered during ECMO varied between 0.0068 mg/kg/h and 0.051 mg/kg/h. During the first 11 days of ECMO follow-up, ACT was maintained within the target range, with a mean value of 164 seconds. After day 12, anticoagulation monitoring was performed only with aPTT because ACT cartridges were unavailable; from day 12 onward,

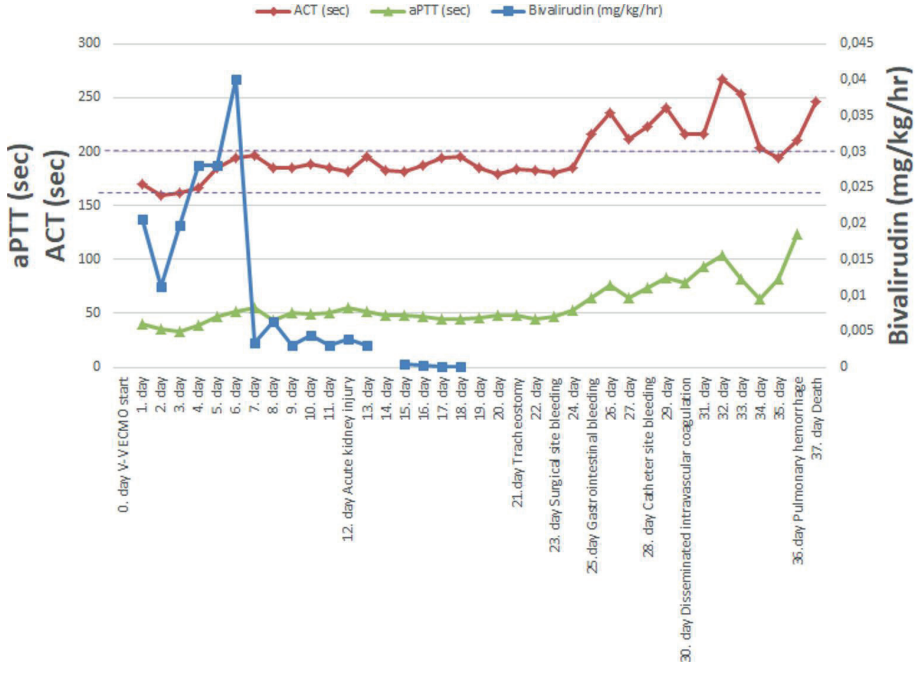

Figure 3. Case 3 clinical events timeline.

ACT target range:160-200 sec, aPTT target range: 50-70sec, ACT (mean): 197sec, aPTT(mean):58sec.

the mean aPTT was 50 seconds and remained within the target range. On day 21, the bivalirudin infusion was discontinued, and a percutaneous tracheostomy was performed on day 22. ECMO support was terminated on day 23. An ischemic cerebrovascular event developed on day 28. Subsequently, left-sided pneumothorax developed on day 29, sepsis on day 30, and right-sided pneumothorax on day 31. During follow-up, mechanical ventilatory support was discontinued on day 45, the tracheostomy was closed on day 47, and the patient was discharged home on day 61.

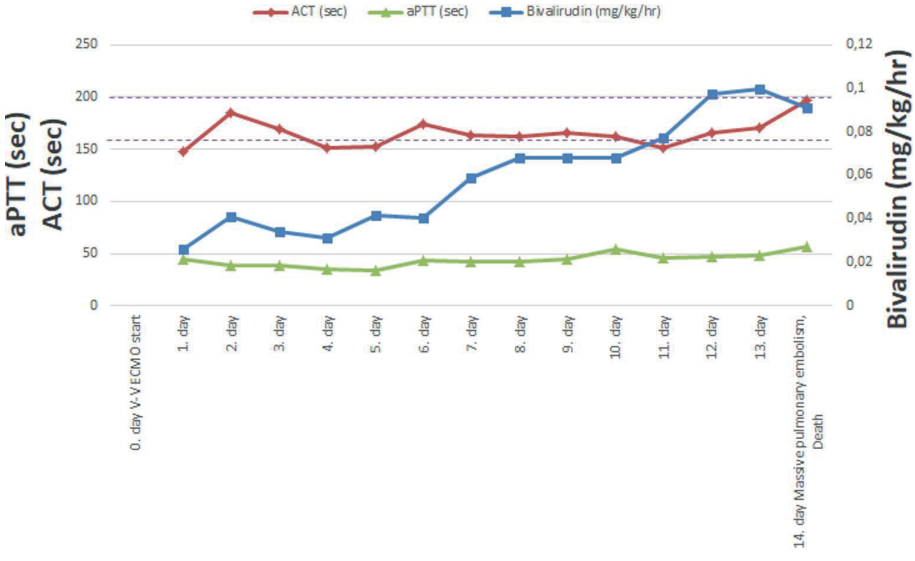

Figure 4. Case 4 clinical events timeline.

ACT target range:160-200 sec, aPTT target range: 50-70sec, ACT (mean): 166sec, aPTT(mean):44sec.

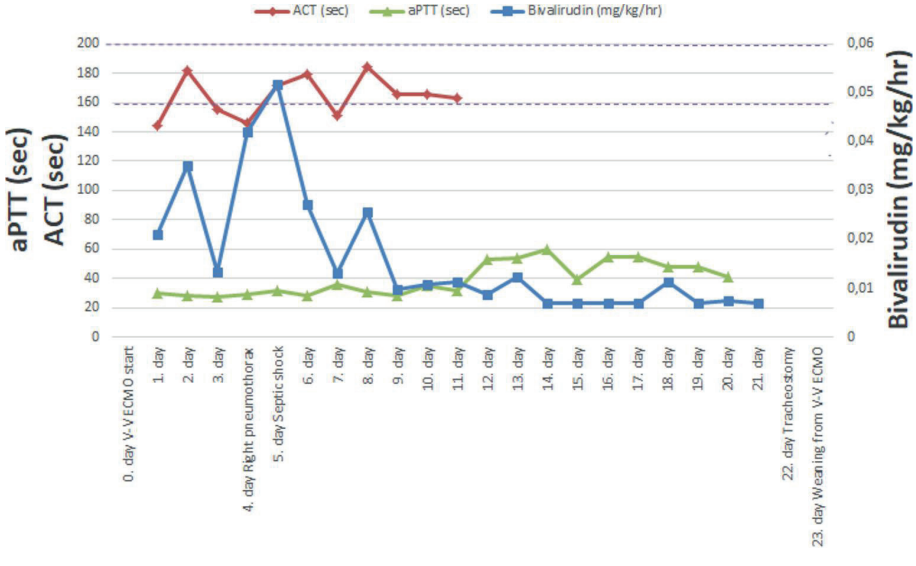

Figure 5. Case 5 clinical events timeline.

ACT target range: 160-200 sec, aPTT target range:50-70sec, ACT (mean): 164sec, aPTT(mean):40sec.

Case 6

The sixth case was a 40-year-old female patient. The clinical events timeline of the case is shown in Figure 6. The daily mean bivalirudin dose administered during ECMO varied between 0.01 mg/kg/h and 0.057 mg/kg/h. Throughout ECMO, ACT was maintained within the target range, with a mean value of 174 seconds. The mean aPTT was 58 seconds and was within the target range. However, gastrointestinal bleeding occurred on day 10 while ACT and aPTT values were within the target ranges, and catheter-site bleeding was observed on day 12. Until bleeding was controlled, ACT was maintained close to a target value of 150 seconds. ECMO support was terminated on day 22. A percutaneous tracheostomy was performed on day 23. Mechanical ventilatory support was discontinued on day 32, the tracheostomy was closed on day 35, and the patient was discharged home on day 43.

Discussion

This case series presents the follow-up and outcomes of patients who received bivalirudin as an anticoagulant during ECMO support.

Over the last decade, an increasing body of evidence regarding the use of bivalirudin as an anticoagulant in ECMO has demonstrated its safety during ECMO support, and emerging data suggest that it provides a superior balance between thrombosis and hemorrhage (11). A retrospective study involving 32 pediatric ECMO patients demonstrated fewer bleeding complications with bivalirudin use (12). Current studies have reported that bivalirudin use achieves therapeutic anticoagulation targets in a shorter time, maintains patients within the therapeutic range for longer periods, and results in less variation in aPTT levels (13).

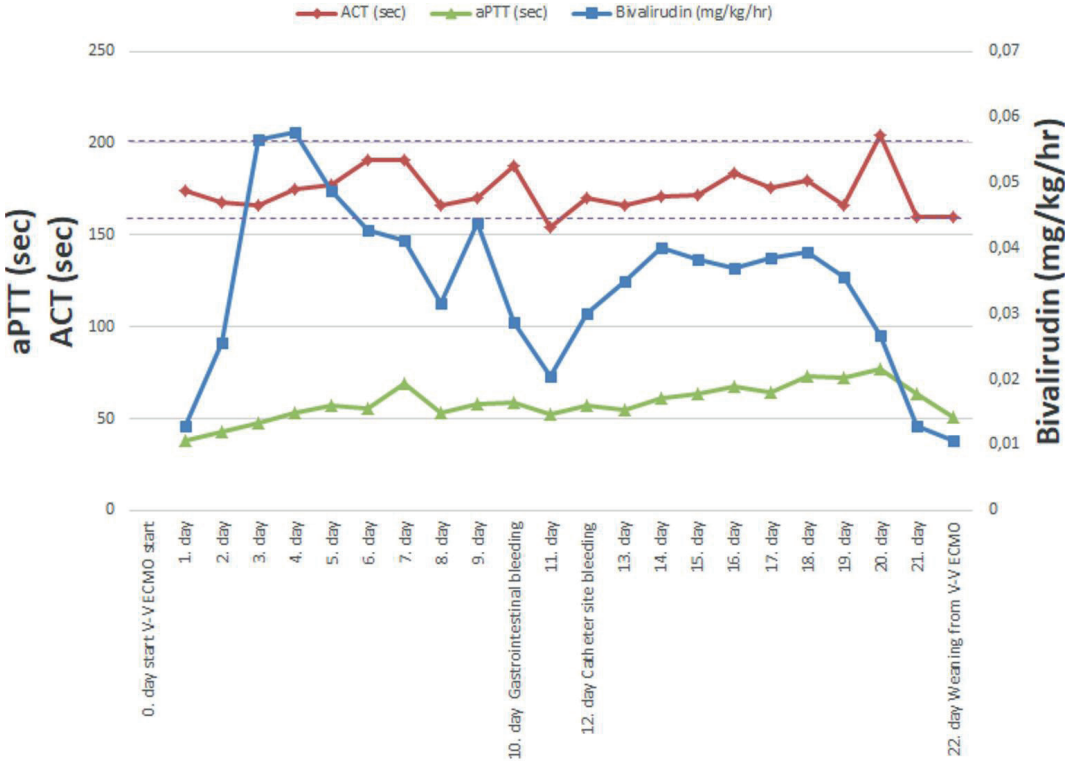

Figure 6. Case 6 clinical events timeline.

ACT target range:160-200 sec, aPTT target range:50-70 sec, ACT (mean): 174sec, aPTT(mean):58sec.

Although aPTT is recommended for monitoring anticoagulation with Direct Thrombin Inhibitors (DTIs), it has been reported that at high DTI concentrations, aPTT values may underestimate the actual anticoagulant effect. Furthermore, in patients receiving DTIs, elevated factor VIII or fibrinogen levels may lead to inaccurate aPTT results; therefore, alternative tests have been recommended. Since this situation may result in an underestimation of bleeding risk, ACT monitoring has been suggested for DTI anticoagulation management (14).

The ELSO guidelines state that ACT may be used to monitor trends in DTI anticoagulation. Experience in interpreting ACT results without adhering to a strict numerical range may enhance the utility of this test. Since each anticoagulation assay has its own advantages and disadvantages, ELSO recommends that anticoagulation efficacy should be monitored using a patient-specific protocol regardless of the anticoagulant agent used, and that both a plasma-based test (aPTT) and a whole-blood hemostatic test (ACT) should be available in clinical practice (15).

In our case series, in addition to aPTT, which is the standard test recommended for monitoring bivalirudin therapy, ACT monitoring was also performed because it was more suitable for our daily clinical practice and provided rapid results. Studies are also available in the literature in which the anticoagulant effect of bivalirudin was monitored solely using ACT values (16). In all of our cases, ACT values remained within the target range. However, mean aPTT values remained below the target range in four cases, whereas bleeding complications developed in Cases 3 and 6, whose mean aPTT values were within the target range. These findings support the notion that aPTT values may underestimate the true anticoagulant effect at high DTI concentrations (15).

The 2021 ELSO guidelines recommend measuring ACT every 1–2 hours and aPTT every 6–12 hours during ECMO anticoagulation monitoring (15). There are also studies recommending aPTT monitoring every 2–4 hours initially for bivalirudin therapy and once daily after achieving the target range (17). In our clinical practice, we followed the recommendations of the 2021 ELSO guidelines regarding the frequency of anticoagulation testing.

In Case 6, gastrointestinal bleeding and catheter-site bleeding complications were controlled by reducing the bivalirudin dose. However, in Case 3, the dose was initially reduced following the development of acute kidney injury on day 12. In the following days, as the patient required renal replacement therapy and continued to exhibit elevated ACT levels and persistent bleeding complications, the bivalirudin infusion was discontinued. It is known that the half-life of bivalirudin is prolonged in severe renal failure (18,19), and dose adjustment is recommended in patients who develop severe renal dysfunction (9,20). Therefore, the elevated ACT and aPTT values observed in this patient may be associated with acute kidney injury.

Another important complication during ECMO support is the tendency toward thrombosis. This has been reported more frequently, particularly in COVID-19 patients with a predisposition to coagulopathy, as in our case series (21,22). In our series, Case 4 developed a massive pulmonary embolism despite ACT values remaining within the target range, and Case 5 experienced an ischemic cerebrovascular event after ECMO discontinuation. However, aPTT values in both patients remained below the target range. The thrombotic complications observed may be related to this finding; however, the occurrence of bleeding complications in two patients whose aPTT values were within the target range makes this hypothesis debatable.

The incidence of thrombotic complications has been reported to be 20–30% among hospitalized COVID-19 patients (23). In the study by Arachchillage et al., thrombosis was detected in 63% of ECMO patients, with pulmonary embolism being the most common thrombotic complication, occurring in 26.9% of patients. In the same study, bleeding complications

occurred in 30.9% of patients, of which 10.9% were intracranial hemorrhages (24). In the study conducted by Shaefi et al. among COVID-19 patients receiving ECMO support, thrombotic events occurred in 22.6% of cases, whereas bleeding complications were observed in 27.9% of patients. While thrombotic events were not shown to have a statistically significant effect on mortality, bleeding complications were found to be significantly associated with mortality (25).

A study comparing bivalirudin and UFH during ECMO demonstrated a lower bleeding rate in the bivalirudin group (26). In a more recent study, when thrombotic events, bleeding events, and total blood product replacement requirements were evaluated together, bivalirudin appeared to be more advantageous than UFH in patients receiving ECMO support. In that study, red blood cell and fresh frozen plasma transfusion requirements were significantly lower in the bivalirudin group compared with the UFH group. Notably, among patients in the bivalirudin group, all of whom had COVID-19, no increase in thrombotic events was observed despite the known prothrombotic tendency associated with COVID-19 (27). In another study involving patients receiving ECMO support following post-cardiotomy shock, fresh frozen plasma and platelet transfusion requirements were significantly lower in the bivalirudin group compared with the UFH group, whereas red blood cell transfusion requirements were similar between the two groups (28). Based on these literature data, bivalirudin may be considered a suitable alternative anticoagulant in patients receiving ECMO support due to COVID-19.

There is considerable variability in the reported bivalirudin dose required to achieve effective anticoagulation. In a case series by Halawi et al., the bivalirudin dose required for effective anticoagulation ranged between 0.05 and 0.1 mg/kg/h (29). Another study reported that the required bivalirudin dose varied between 0.02 and 0.5 mg/kg/h (30). In our case series, the bivalirudin dose required to achieve the target ACT ranged between 0.01 and 0.2 mg/kg/h, which was lower than that reported in the literature. Similarly, in the study by Macielak et al., bivalirudin infusion doses ranged from 0.01 to 0.05 mg/kg/h, and the target ACT was maintained between 160 and 180 seconds (31).

Conclusion

In conclusion, this case series suggests that bivalirudin may be used as an alternative anticoagulant for the prevention of thrombotic events in patients receiving V-V ECMO support for ARDS. Nevertheless, regardless of the anticoagulant agent used or the monitoring method employed, bleeding and thrombosis remain important complications during V-V ECMO therapy. Therefore, close monitoring and individualized anticoagulation management are required to optimize patient outcomes. Larger-scale studies are needed to evaluate the efficacy of bivalirudin and to determine the effectiveness of monitoring strategies, particularly in V-V ECMO patients with underlying diseases that predispose them to coagulopathy.

Ethical approval

This study has been approved by the Non-Invasive Research Ethics Committee of Sakarya University (approval date: 02.06.2022, number: 71522473-050.01.04-136950-156). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: ÖK, KÖS, AFE, FT; data collection: ÖK, KÖS, MGK; analysis and interpretation of results: ÖK, KÖS; draft manuscript preparation: ÖK, KÖS. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE SERIES

Heterogeneous clinical spectrum of severe methanol poisoning in the intensive care unit: a case series from full recovery to brain death

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ABSTRACT

Methanol, a toxic substance, has been identified as a causative agent for lethal poisoning. The present case series includes nine patients admitted to the intensive care unit (ICU) due to methanol poisoning between 25th November 2024 and 13th January 2025. The median age of the patients was 49 (43-54) years, with eight of them being male. All patients exhibited high anion gap metabolic acidosis and underwent renal replacement therapy. The majority of the patients received a combination of ethanol and folinic acid therapies. It is noteworthy that a third of patients experienced a cardiopulmonary arrest either in their own homes or in the immediate period following their admission to the hospital. Six patients survived to ICU discharge: four were transferred to hospital wards or discharged from the hospital, and two were transferred to palliative care units. One patient died shortly after ICU admission, another died during prolonged ICU follow-up, and one was diagnosed with brain death and subsequently underwent organ procurement surgery. In conclusion, a deteriorated neurological state, receipt of cardiopulmonary resuscitation, and the presence of pathological findings in radiological imaging of the central nervous system, cardiac injury, vasopressor requirement, sepsis, and ventilator-associated pneumonia were likely to be associated with an increased risk of poor outcomes.

Keywords: acidosis, alcohols, methanol, poisoning, toxicity

Introduction

Methanol, a chemical compound with a wide range of industrial applications as a solvent (1), has been identified as a causative agent of lethal poisoning (2). Even relatively minor ingestions have the potential to induce severe toxicity (3). Documented cases of inhalational and dermal toxicity have also been reported (2). However, consumption of unlabeled or home-made alcohol-based beverages has also been identified as a risk factor for methanol poisoning (1).

The underlying mechanism of methanol poisoning is associated with its acid metabolites, particularly formate. This association has been linked to a range of serious health consequences, including retinal damage with optic disc edema and/or hyperemia, ischemic or hemorrhagic damage in the basal ganglia, particularly in the putamen, and white matter of the insular subcortex and renal toxicity (1,4,5). These changes manifest with a range of complaints, including central nervous system (CNS) suppression, blurred vision, blindness, seizures, coma and acute kidney failure (1,3-6). The diagnosis of patients with methanol poisoning is based on strong suspicion (1-3). The presence of a persistent metabolic acidosis with a high anion gap, a large osmolal gap and impaired kidney function are the additional clinical conditions (3). Despite the implementation of

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interventions such as ethanol or fomepizole to inhibit alcohol dehydrogenase (ADH), and extracorporeal treatments, the prognosis for patients with methanol poisoning remains uncertain (3). The mortality rate associated with methanol poisoning ranges from 16% to 48% in the literature (7,8).

In this case series, we present the clinical characteristics of nine patients with methanol poisoning. The patients exhibited comparable clinical scenarios, yet their outcomes were influenced by distinct factors.

Case series

This case series examined a cohort of nine patients admitted to our center's intensive care units (ICUs) with methanol intoxication between November 25, 2024, and January 13, 2025. The median age of the patients was 49 (43–54) years, and the majority were male (88.9%), as detailed in Table 1. The median Charlson comorbidity index and the acute physiology and chronic health evaluation II scores were 0 (0–1) and 26 (15–36), respectively. The median Glasgow coma scale (GCS) score of the patients was 9 (3–15). The median duration from the onset of symptoms to hospital admission was 9 (2–39) hours. The median length of hospital and ICU stay was determined to be 8 (3–63) days and 3 (2–61) days, respectively.

Patient 1

A 53-year-old male patient was discovered unresponsive in his home environment by his family members and was administered cardiopulmonary resuscitation. The patient was intubated by the ambulance crew and transferred to the emergency department. On admission, ventricular fibrillation was detected. Subsequent to the defibrillation, the cardiac massage was continued for a further duration of 30 minutes. Following the return of spontaneous circulation, the infusion of noradrenaline was initiated in order to treat refractory hypotension. Coronary angiography was performed with a preliminary diagnosis of acute coronary syndrome, but coronary perfusion was found to be normal. The results of the blood gas analysis indicated the presence of high anion gap metabolic acidosis (Table 2). In addition to the findings from the laboratory, the patient was primarily suspected of methanol poisoning, as family members reported that the patient had consumed alcoholic-based homemade beverages. Subsequently, a loading dose of 4 mL/kg of 20% ethanol was administered orally, followed by a maintenance infusion at a rate of 0.8 mL/kg/hour for a period of 72 hours. Additionally, intravenous sodium bicarbonate infusion initiated a rate of 1 mEq/kg. Following a two-hour session of conventional

Table 1. Patient characteristics.

Characteristics	All (n = 9)	Patients								
		I	II	III	IV	V	VI	VII	VIII	IX
Age, years	49 (43–54)	53	39	55	48	49	43	50	42	57
Sex, male	8 (88.9)	Male	Male	Male	Male	Female	Male	Male	Male	Male
APACHE II score[a]	26 (15–36)	36	3	9	25	20	26	42	35	27
CCI	0 (0–1)	1	0	1	0	0	0	1	0	1
GCS[a]	9 (3–15)	3	14	15	14	15	3	3	4	9
Length of duration										
First symptom to hospital admission, hours	9 (2–39)	N/A	48	6	1	48	12	1	4	12
Hospital stay, days	8 (3–63)	263	2	66	3	8	4	59[b]	1	28
ICU stay, days	3 (2–61)	263	2	62	2	2	4	59	1	3

All values are expressed as numbers (percentages) or median (interquartile range).
APACHE II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; GCS, Glasgow Coma Scale; N/A, not applicable.
[a]Calculated on the day of hospital admission.
[b]The patient was transferred to a palliative care unit in another center.

Table 2. Laboratory data of the patients.

Laboratory test	Alla (n = 9)	Patients								
		I	II	III	IV	V	VI	VII	VIII	IX
BUN, mg/dL	14.4 (12.1–16.7)	13.5	14.4	14.4	18.0	6.0	10.7	25.2	15.4	13.5
Creatinine, mg/dL	1.21 (1.02–1.52)	1.10	1.09	0.95	1.21	0.74	1.42	2.00	1.60	1.44
Na, mmol/L	140.0 (138.8–142.0)	139.0	141.0	139.0	140.0	144.0	143.0	137.6	140.0	138.5
Cl, mmol/L	110 (108–112)	110	109	113	105	108	108	111	111	114
K, mmol/L	4.87 (3.87–5.50)	3.46	4.87	5.53	4.37	5.35	3.75	7.79	3.98	5.47
Serum Ethanol, mg/dL	N/A	58.4	< 10	< 10	< 10	< 10	< 10	< 10	12.2	< 10
Blood gas analysis										
pH	7.04 (6.74–7.12)	7.04	7.15	7.15	7.05	7.08	6.78	6.7	6.94	6.7
PCO_2, mmHg	30.2 (26.7–34.9)	35.8	27.3	23.7	33.9	26.2	27.1	30.2	34.0	41.3
PaO_2, mmHg	159 (112–269)	191	144	198	159	82	339	482	101	122
HCO_3, mmol/L	9.4 (4.6–10.6)	9.7	10.9	11.1	10.3	9.4	3.9	4.2	7.5	5.0
BE	-21.5 (-31.1–-20.7)	-20.8	-19.7	-20.6	-21.2	-21.5	-31.0	-32.4	-26.5	-31.2
Lactate, mmol/L	6.9 (1.3–8.5)	11.1	0.9	0.2	7.5	1.7	9.4	7.3	2.8	6.9
SO_2, %	98 (96–99)	98	98	98	99	96	99	100	96	94
PaO_2 / FiO_2	328 (310–361)	202	342	301	318	380	335	441	318	328
Anion gap	29.1 (23.9–32.3)	22.8	26.0	20.4	29.1	32.0	34.9	30.2	32.5	25.0

All values are presented as median and interquartile range or numbers.
BUN, blood urea nitrogen; N/A, not applicable; PCO_2, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; BE, base excess; SO_2, oxygen saturation; FiO_2, fraction of inspired oxygen.
[a]Calculated based on laboratory test results performed on hospital admission.

hemodialysis in the emergency department, the patient was transferred to the intensive care unit (ICU) to initiate continuous renal replacement therapy (CRRT), in addition to other supportive therapies. Furthermore, folinic acid (4 x 50 mg) was prescribed for three days. However, fomepizole therapy was not administered due to a lack of availability. The metabolic abnormalities were resolved after several days. However, CRRT was administered for a duration of 360 hours due to acute renal failure. The patient's unconsciousness was attributed to hypoxic-ischemic encephalopathy, as evidenced by cerebral magnetic resonance imaging (MRI). The patient also suffered from ventilator-associated pneumonia (VAP), sepsis, and cardiac injury. The patient underwent a tracheostomy procedure and was provided with a home-type mechanical ventilator. A percutaneous endoscopic gastrostomy (PEG) tube was inserted for the purpose of enteral feeding. However, the patient died on the 263rd day of hospital admission due to septic shock.

Patient 2

A 39-year-old male patient was admitted to hospital with complaints of nausea, vomiting and blurred vision. On admission, the Glasgow Coma Scale (GCS) score was 14. It was reported by the patient's family that his mental state had deteriorated since the onset of symptoms, and that he had consumed large quantities of alcoholic, homemade beverages over the previous two days. The results of the laboratory tests indicated the presence of two key pathologies: high anion gap metabolic acidosis and acute kidney injury. Following a two-hour session of conventional hemodialysis in the emergency department, the patient was transferred to the ICU. Furthermore, sodium bicarbonate infusion was administered. In the intensive care unit, metabolic abnormalities were

resolved after the initiation of several hours of CRRT. The patient was discharged from hospital on the second day of ICU admission.

Patient 3

A 55-year-old male patient diagnosed with hypertension was admitted to the emergency department with complaints of nausea, vomiting, confusion, and blurred vision. It was reported that the patient consumed homemade alcohol-based beverages six hours prior to admission. On admission, the GCS score was 15. The laboratory tests revealed a high anion gap metabolic acidosis reflecting methanol poisoning. The patient was subsequently transferred to the ICU. On ICU admission, the GCS score was documented as 11. Intravenous 10% ethanol was initiated with a loading dose of 10 mL/kg over 60-minute period, followed by a maintenance dose of 1 mL/kg per hour for a duration of 72 hours. Furthermore, the patient received a sodium bicarbonate infusion at a dose of 1 mEq/kg for a duration of 10 hours. Following the administration of CRRT, the patient required noradrenaline infusion due to hypotension. Following a period of several hours, there was a deterioration in the patient's mental state, which resulted in a decrease in the GCS score to 7. The patient was intubated to ensure optimal airway safety. The cerebral diffusion MRI revealed restricted perfusion in bilateral supratentorial and infratentorial areas. The therapeutic approach of anti-antiaggregant therapy was initiated in the management of acute ischemic cerebrovascular disease. It was observed that by the third day of admission to the intensive care unit (ICU), metabolic abnormalities had been resolved. However, CRRT was required to be administered for a duration of 432 hours due to anuria. During the patient's hospitalization period in ICU, sepsis, cardiac injury, and VAP were observed as complications. The patient underwent a tracheostomy procedure and was provided with a home-type mechanical ventilator. A PEG tube was inserted for the purpose of enteral feeding. Following a period of 62 days in the intensive care unit, the patient was discharged to the palliative care unit.

Patient 4

A 48-year-old male patient was admitted to hospital with symptoms of chest pain, and paresthesia in the upper limbs. On admission, the GCS score was 14. The laboratory tests revealed high anion gap metabolic acidosis. As reported by the patient's family, the patient had consumed alcohol-based beverages, prepared in the home, a few hours prior to admission. In the emergency department the patient was intubated as a consequence of a loss of consciousness. Following a two-hour hemodialysis session, the patient was transferred to the ICU. The intravenous administration of 10% ethanol was initiated with a loading dose of 10 mL/kg over a 60-minute period, followed by a maintenance dose of 1 mL/kg per hour for a duration of 48 hours. Furthermore, the patient received a sodium bicarbonate infusion at a dose of 1 mEq/kg for a duration of 6 hours and folinic acid therapy (4 x 50 mg, for three days). The metabolic abnormalities were resolved with no requirement for additional CRRT. On the second day of admission to the ICU, the patient was extubated and subsequently transferred to a ward one day later.

Patient 5

A 49-year-old female patient suffering from hypertension was admitted to the emergency department, presenting with symptoms including headache and blurred vision. The onset of these symptoms was reported to have occurred 48 hours prior, following the consumption of homemade alcohol-based beverages. At the time of admission, the GCS score was recorded at 15. The laboratory test revealed a high anion gap metabolic acidosis, indicative of methanol poisoning. The sodium bicarbonate infusion was initiated with an initial dose of 1 mEq/kg, with the infusion continuing for a duration of 6 hours. Following a two-hour session of conventional hemodialysis, the patient was transferred to the ICU. In the ICU, a loading dose of 4 mL/kg of 20% ethanol was administered orally, followed by a maintenance infusion at a rate of 0.8 mL/kg/hour for a period of 24 hours. Furthermore, the patient received folinic acid

therapy 50 mg every six hours for three days. The therapeutic interventions previously mentioned have been shown to be effective in resolving metabolic abnormalities, thereby negating the necessity for CRRT. On the second day of admission to the ICU, the patient was discharged from the ICU to the internal medicine ward.

Patient 6

A 43-year-old male patient was admitted to the hospital after presenting with symptoms including vomiting, dizziness, impaired speech, and loss of consciousness following the consumption of homemade alcohol-based beverages twelve hours prior. The patient had a medical history of hypertension, hyperlipidemia, and atrial arrhythmia. The patient was intubated in view of a deteriorated neurological state. The blood gas analysis revealed a high anion gap metabolic acidosis indicative of methanol poisoning. A sodium bicarbonate infusion was initiated with a dose of 1 mEq/kg. Concurrently, during the patient's conventional hemodialysis treatment, a generalized tonic-clonic seizure manifested. The seizure was successfully managed by the administration of antiepileptic medication, and hemodialysis therapy was interrupted during the first hour of the session. Following the conducting of a cerebral computed tomography (CT) scan, the patient was transferred to the ICU. A neurological examination was conducted on the patient upon their admission to the ICU, and it was found that the patient lacked a pupillary light reflex. The CT scan revealed a widespread cerebral oedema. The neurosurgical team determined that the patient was not suitable for surgical intervention. The enteral solution of 20% ethanol was administered at a dose of 4 ml/kg, with a subsequent maintenance dose of 0.5 ml/kg/h over a 48-hour period. In order to address metabolic acidosis, the CRRT was initiated. A neurological examination conducted in the 72nd hour of ICU follow-up revealed the absence of brain stem reflexes. A subsequent apnea test resulted in a diagnosis of brain death. A contrast-enhanced CT cerebral angiography revealed a lack of cerebral perfusion. The patient underwent a surgical procedure involving the donation of a liver, heart and kidneys on the 4th day of admission to the ICU.

Patient 7

A 50-year-old male patient suffering from hypertension was found unresponsive and was taken to hospital by his family. Following admission, the neurological examination revealed the presence of dilated pupils with no light reflex, and a GCS score of 3. The patient was intubated for the aforementioned reasons. As reported by the patient's family, the patient was engaged in the production of alcoholic beverages within the domestic environment. In addition, empty bottles of homemade alcoholic beverages were discovered in the immediate vicinity of the patient. The laboratory tests revealed a high anion gap metabolic acidosis. The infusion of sodium bicarbonate was initiated at a rate of 1 mEq/kg intravenously. The patient underwent conventional hemodialysis. However, the patient suffered from cardiopulmonary arrest during hemodialysis therapy. The patient was transferred to the ICU after the ROSC within a period of 9 minutes cardiopulmonary resuscitation. After ROSC the patient also required vasopressor support. In the ICU, the CRRT was initiated. Furthermore, intravenous 10% ethanol therapy was initiated, with a loading dose of 10 mL/kg over a 60-minute period, followed by a maintenance dose of 1 mL/kg per hour for a duration of 48 hours. Additionally, folinic acid therapy was administered for 50 mg every six hours for three days. On the 2nd day of ICU admission, the patient exhibited myoclonic jerks that were successfully controlled by antiepileptic medications. However, subsequent MRI scan results revealed restricted diffusion in both cerebral hemispheres, in all lobes, in cortico-subcortical regions and basal ganglia, in the posterior fossa, in both cerebellar regions, and microbleeds in bilateral basal ganglia. Subsequent to the passage of several days, the metabolic abnormalities were resolved. However, the patient received CRRT for a period of ten days due to anuria. During the patient's stay in the ICU, additional complications were

observed, including cardiac injury, sepsis, and VAP. Consequently, the patient underwent tracheostomy and PEG procedures due to a poor neurological state and was discharged to the palliative care unit with home type MV support on the 59th day of hospital admission.

Patient 8

A 42-year-old male patient was transferred to the emergency department by his family, exhibiting symptoms that included a loss of consciousness subsequent to the ingestion of domestically prepared alcoholic beverages. Upon admission, the GCS was recorded as 4, and the patient underwent cardiopulmonary resuscitation for a duration of 5 minutes. After ROSC, the patient required vasopressor support with noradrenaline infusion at a rate of 0.4 mcg/kg/min. The laboratory tests revealed a high anion gap metabolic acidosis. In the emergency department, intravenous sodium bicarbonate infusion was initiated at a rate of 2 mEq/kg. Following a two-hour session of conventional hemodialysis, the patient was transferred to the ICU. The CRRT therapy was initiated in the ICU. In addition, folinic acid therapy was prescribed 50 mg every six hours. Despite the interventions undertaken, the patient died several hours after being admitted to the ICU due to refractory hypotension and metabolic acidosis that did not improve despite all supportive treatments, prior to the administration of intravenous or enteral ethanol therapy.

Patient 9

A 57-year-old male patient was transferred to the emergency department by ambulance, reporting a complaint of confusion and vision loss. On admission, the GCS score was documented as 9. However, the patient was intubated due to the neurological deterioration half an hour later. The ambulance crew reported finding empty bottles in the patient's environment that could potentially be linked to homemade alcohol-based beverages. The laboratory test revealed a high anion gap metabolic acidosis, indicating methanol poisoning. An infusion of sodium bicarbonate was initiated at a rate of 1 mEq/kg. Following a two-hour session of conventional hemodialysis, the patient was transferred to the ICU. In the ICU, the intravenous administration of 10% ethanol was initiated with a loading dose of 10 mL/kg, followed by a maintenance dose of 1 mL/kg/hour for a period of three days. Furthermore, folinic acid was prescribed for a period of three days (4 x 50 mg). Following a 24-hour period of ICU admission, the patient was successfully weaned from mechanical ventilation. Furthermore, the CRRT was terminated on the third day of ICU admission. Nevertheless, the patient continued to exhibit symptoms of oliguria. The patient was transferred to the nephrology ward two days after weaning, with a GCS score of 15.

Written informed consent for publication of this case series was obtained from the patients or their next of kin.

Discussion

The present case series, which analyzes a cohort of nine patients treated in the ICU due to methanol poisoning, reveals that four of the survivors were discharged from the ICU with normal neurological status and kidney function. However, two of the patients exhibited poor neurological outcomes, and one patient died immediately after ICU admission without achieving further treatment modalities and radiological analysis, while another in the late period of ICU follow-up. Notably, one patient was diagnosed with brain death and underwent kidney, heart, and liver donation surgery.

In patients admitted to the hospital with methanol poisoning, Kussmaul breathing (6) and gastrointestinal symptoms, including nausea, vomiting, and abdominal pain, are often the initial manifestations (1,8). Furthermore, patients may present with symptoms of CNS suppression, including confusion, drowsiness, seizures, coma, and visual abnormalities, such as diplopia, photophobia, blurred vision (1-3,6,8), early or late blindness, and nystagmus (1-3).

Pupillary mydriasis with delayed or no response to light is another manifestation (1,8). The most prevalent presentations in this case series were those of CNS suppression and visual abnormalities, which were associated with severe intoxication (3).

The diagnosis of patients with methanol poisoning is largely dependent upon a high degree of suspicion or clear evidence of ingestion (1-3). Laboratory findings, specifically blood gas analysis indicating acidosis with a high anion gap, enlighten to the diagnosis (1,2). Increased levels of lactate may also contribute to the extension of anion gap (2). Impaired kidney function tests or elevated osmolal gap levels may also support the diagnosis (1-3). However, the direct measurement of serum methanol or formate levels, which is based on gas chromatographic analysis, is important for rapid clinical decision-making. Unfortunately, these measures are not widely available in many healthcare facilities (1,9). In the present case series, the ingestion of home-made alcohol-based beverages was confirmed by patients, family members, or patient's friends. Blood gas analysis indicated a high anion gap metabolic acidosis for all patients on hospital admission and acute kidney injury was present for all patients on admission or during their hospital stay. The direct measurement of serum methanol level is only available as a "send out-test" in our center, and it is not suitable for the rapid clinical decision-making. Furthermore, at the time of admission of these patients in this case series, clinicians had a clear perception of a multi-victim methanol poisoning outbreak. This perception also facilitated the diagnosis of methanol poisoning.

The initial treatment of patients with methanol poisoning should prioritize airway safety (1,2). Ensuring a brief apneic phase during rapid sequence intubation, particularly in patients with severe metabolic acidosis, may reduce the risk of complications related to intubation (10). The treatment of hypotension involves the administration of crystalloids (1,2) and/or vasopressors (2). It is noteworthy that two-thirds of the patients in the present case series required invasive mechanical ventilation and almost as many vasopressor requirements. The primary treatment strategy for patients with methanol poisoning involves the inhibition of ADH by fomepizole or ethanol to prevent further metabolism of methanol to formate (1,2,8). However, due to unavailability of fomepizole, this treatment option could not be provided to the patients in the present case series. Nevertheless, ethanol treatment was administered intravenously or enterally to the patients. However, a study analyzing risk factors for the poor outcomes in patients with methanol poisoning revealed that fomepizole therapy is more effective than ethanol therapy among these patients (10). Notably, *patient II* did not require ethanol therapy after conventional HD, while *patient VIII* died immediately after admission without receiving ethanol therapy. Consequently, healthcare facilities should be adequately prepared to administer ethanol or fomepizole therapies at the earliest stages of patient admissions, particularly during periods of multi-victim poisoning outbreaks. In patients suffering from methanol poisoning, bicarbonate facilitates the process of formate dehydronation, thereby enabling excretion in the urine rather than penetration into end-organ tissues (1,2). In a similar manner, folinic acid administration has been shown to enhance formate metabolism to carbon dioxide and water (1,2,8). In the present case series, all patients received bicarbonate therapy, while folinic acid therapy could not be administered to four of them. We hypothesized that the efficacy of folinic acid therapy would be limited due to the critical condition of *patient VIII*, who did not receive this treatment. However, *patient VI*, another patient who did not receive folinic acid therapy and was diagnosed with brain death, provides an exception to this observation. Continuous renal replacement or conventional HD therapies are the optimal treatment options for the elimination of methanol and its metabolites. The administration of extracorporeal therapies is recommended in cases of severe poisoning, characterized by symptoms such as coma, seizures, visual abnormalities, and metabolic acidosis with a pH <7.15, an anion gap

>24 mmol/L, or persistent acidosis despite adequate therapy or antidotes. Furthermore, in the context of fomepizole and ethanol therapies, serum methanol concentrations of >700 mg/L (21.8 mmol/L) and >600 mg/L (18.7 mmol/L) are considered decision thresholds for the initiation of HD administration, respectively. However, it is important to note that plasma exchange, hemoperfusion, and peritoneal dialysis are not recommended since these treatment modalities have been demonstrated to be ineffective for the clearance of methanol and its metabolites. Furthermore, clinical improvement or methanol concentration <200 mg/L (6.2 mmol/L) are considered decision points for discontinuing extracorporeal therapies (3).

A comprehensive review of the studies analyzing patients with methanol poisoning reveals that high osmolal or anion gap (11), low levels of pH (10,11), inadequate respiratory compensation of metabolic acidosis (10), respiratory arrest (12), low levels of GCS score (13), presence of coma (10), hypothermia (13), hyperglycemia (12), increased levels of serum creatinine (13), and length of duration from methanol intake to hospital admission (12) have been identified as risk factors associated with poor outcomes or mortality. In the present case series, a deteriorated neurological state, and/or low GCS score on admission, undergoing cardiopulmonary resuscitation prior or after admission, and the presence of pathological findings in radiological imaging of the CNS are likely to be associated with an increased risk of mortality and poor neurological outcome. Furthermore, major events such as cardiac injury, vasopressor requirement, sepsis, and ventilator-associated pneumonia might be additional risk factors.

Ethical approval

Written informed consent for publication of this case series was obtained from the patients or their legal representatives.

Author contribution

Study conception and design: MNY, OD, MA; data collection: FOD, BB, ÖA, BK, CY, OA; analysis and interpretation of results: MNY, OD, MA; draft manuscript preparation: FOD, MNY; critical review of the manuscript for important intellectual content: FOD, BB, ÖA, OD, BK, CY, OA, MA. All authors approved the final version for publication and agreed to be accountable for all aspects of the work, including ensuring that any questions regarding its accuracy or integrity are appropriately investigated and resolved.

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Conflict of interest

The authors declare that there is no conflict of interest.

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