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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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Conflict of interest

The authors declare that there is no conflict of interest.

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