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Original Research Article

Drug–Drug Interactions (DDIs) Involving Commonly Used ICU Drugs: Prevalence and Clinical Consequences

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Abstract: Critically ill patients admitted to intensive care units (ICUs) are frequently exposed to multiple medications, particularly vasopressors, sedatives, and antimicrobials. Polypharmacy, altered pharmacokinetics, and organ dysfunction predispose these patients to drug–drug interactions (DDIs), which may adversely affect clinical outcomes. However, the overall prevalence and clinical impact of DDIs involving commonly used ICU drugs have not been comprehensively quantified. ***Objectives*** To systematically evaluate the prevalence of clinically significant DDIs involving vasopressors, sedatives, and antimicrobials in ICU patients, and to assess their association with adverse clinical outcomes. ***Methods*** A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and Scopus were searched from database inception to January 2025. Observational studies and randomized controlled trials reporting DDIs in ICU settings were included. Two reviewers independently screened studies, extracted data, and assessed risk of bias. Random-effects meta-analysis was used to pool prevalence estimates and effect measures. Heterogeneity was assessed using the I^2 statistic. ***Results*** A total of 38 studies comprising 47,892 ICU patients were included in the systematic review, of which 29 studies were eligible for meta-analysis. The pooled prevalence of clinically significant DDIs was 54.7% (95% CI: 48.9–60.3; I^2 = 89%). Sedative–antimicrobial interactions were most frequent (41.2%), followed by antimicrobial–vasopressor (32.5%) and sedative–vasopressor interactions (26.3%). DDIs were significantly associated with increased mortality (OR 1.48, 95% CI: 1.22–1.79), prolonged ICU length of stay (mean difference 3.1 days, 95% CI: 1.9–4.3), and a higher risk of adverse drug events (OR 2.12, 95% CI: 1.65–2.72). ***Conclusions*** Drug–drug interactions involving vasopressors, sedatives, and antimicrobials are highly prevalent in ICU settings and are associated with significantly worse clinical outcomes, including increased mortality and prolonged ICU stay. These findings emphasize the need for proactive DDI surveillance, multidisciplinary medication review, and robust clinical decision-support systems to enhance medication safety in critically ill patients.

Keywords: Drug–drug interactions; Intensive care unit; Vasopressors; Sedatives; Antimicrobials; Polypharmacy; Systematic review; Meta-analysis.

INTRODUCTION

Critically ill patients admitted to intensive care units (ICUs) are among the most vulnerable populations in modern healthcare due to the severity of illness,

frequent organ dysfunction, and the need for complex pharmacological management. The cornerstone of ICU therapy often includes vasopressors to maintain hemodynamic stability, sedatives and analgesics to facilitate mechanical ventilation and patient comfort, and broad-spectrum antimicrobials to manage severe infections and sepsis [1–3]. While these medications are life-saving, their concurrent administration places ICU patients at a substantially increased risk of drug–drug interactions (DDIs).

Polypharmacy is nearly universal in the ICU, with studies reporting that critically ill patients are exposed to a median of 10–15 medications during their ICU stay [4,5]. This extensive drug exposure, combined with altered pharmacokinetics and pharmacodynamics resulting from critical illness—such as hepatic and renal dysfunction, hypoalbuminemia, capillary leak, and altered drug metabolism—creates a fertile ground for clinically significant DDIs [6,7]. Importantly, DDIs in the ICU are not merely theoretical concerns but have been associated with serious adverse drug events, therapeutic failure, prolonged ICU stays, and increased mortality [8,9].

DDIs are broadly classified into pharmacokinetic interactions, which affect drug absorption, distribution, metabolism, or excretion, and pharmacodynamic interactions, which result from additive, synergistic, or antagonistic effects at the site of action [10]. In the ICU context, pharmacodynamic interactions are particularly concerning. For example, the combined use of sedatives and opioids may lead to excessive central nervous system depression and respiratory compromise, while interactions between vasopressors and certain antimicrobials may precipitate arrhythmias, QT prolongation, or unpredictable hemodynamic responses [11–13].

Vasopressors such as norepinephrine, epinephrine, vasopressin, dopamine, and phenylephrine are routinely administered in septic shock and other forms of circulatory failure [14]. Their effects on vascular tone and cardiac output may be potentiated or attenuated by concomitant sedatives, anesthetic agents, and antimicrobials, particularly those affecting adrenergic signaling or cardiac conduction [15]. Similarly, sedatives commonly used in ICUs—including propofol, benzodiazepines, dexmedetomidine, and opioids—are known to interact with cytochrome P450 enzymes and may alter the metabolism of concurrently administered antimicrobials, leading to either subtherapeutic exposure or drug toxicity [16,17].

Antimicrobials represent another major contributor to DDIs in ICU settings. Broad-spectrum antibiotics, antifungals, and antivirals are frequently initiated empirically and later modified based on microbiological results [18]. Agents such as macrolides, fluoroquinolones, azole antifungals, and certain antivirals are well recognized for their potential to cause clinically significant DDIs through enzyme inhibition, QT prolongation, or additive organ toxicity [19–21]. When combined with vasopressors or sedatives, these interactions may exacerbate cardiovascular instability, neurotoxicity, or renal impairment, particularly in critically ill patients with limited physiological reserve [22].

Despite growing awareness of the problem, the reported prevalence of DDIs in ICU patients varies widely across studies, ranging from 20% to over 80%, depending on study design, patient population, and the method used to identify interactions [23–25]. Many studies rely on electronic interaction-checking databases, which may overestimate clinically relevant DDIs by identifying potential rather than actual harmful interactions [26]. Conversely, studies based solely on documented adverse drug events may underestimate the true burden of DDIs due to underreporting or lack of systematic surveillance [27]. This variability underscores the need for a comprehensive synthesis of available evidence.

Moreover, while individual studies have suggested an association between DDIs and adverse clinical outcomes—such as increased mortality, prolonged mechanical ventilation, longer ICU length of stay, and higher healthcare costs—the strength and consistency of these associations remain unclear [28–30]. To date, no comprehensive systematic review and meta-analysis has specifically focused on DDIs involving vasopressors, sedatives, and antimicrobials—the three most commonly co-administered and clinically critical drug classes in ICU practice.

Therefore, the present systematic review and meta-analysis was undertaken to address this knowledge gap. The primary objective was to estimate the prevalence of clinically significant DDIs involving commonly used ICU drugs, specifically vasopressors, sedatives, and antimicrobials. The secondary objective was to evaluate the association between these DDIs and adverse clinical outcomes, including mortality, ICU length of stay, and drug-related complications. By synthesizing available evidence, this study aims to inform clinical practice, support safer prescribing strategies, and highlight the importance of proactive DDI monitoring in critically ill patients.

MATERIAL AND METHOD

Study Design and Reporting Standards

This study was conducted as a systematic review and meta-analysis to evaluate the prevalence and clinical

consequences of drug–drug interactions (DDIs) involving commonly used intensive care unit (ICU) drugs, specifically vasopressors, sedatives, and antimicrobials. The methodology was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility Criteria

Inclusion Criteria

Studies were considered eligible if they met the following criteria:

1. Conducted in adult or pediatric ICU settings (medical, surgical, or mixed ICUs).
2. Included critically ill patients receiving vasopressors, sedatives, and/or antimicrobials.
3. Reported the prevalence or incidence of DDIs, or evaluated clinical outcomes attributable to DDIs.
4. Reported at least one clinical outcome such as mortality, ICU length of stay, duration of mechanical ventilation, adverse drug events, or hemodynamic instability.
5. Observational studies (prospective or retrospective cohort studies, case–control studies, cross-sectional studies) or randomized controlled trials.
6. Published in peer-reviewed journals in the English language.

Exclusion Criteria

Studies were excluded if they:

1. Were conducted exclusively in non-ICU settings.
2. Were case reports, small case series (<5 patients), editorials, narrative reviews, or conference abstracts without full data.
3. Were animal or in-vitro studies.
4. Did not provide sufficient data to extract prevalence estimates or effect measures related to DDIs.

Information Sources and Search Strategy

A comprehensive literature search was performed in the following electronic databases:

- PubMed/MEDLINE
- Embase
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Web of Science
- Scopus

The search was conducted from database inception to January 2025. Search terms included combinations of Medical Subject Headings (MeSH) and free-text keywords related to drug–drug interactions, intensive care units, vasopressors, sedatives, and antimicrobials. The reference lists of all included studies and relevant reviews were manually screened to identify additional eligible studies.

A representative PubMed search strategy was as follows:

(“drug–drug interaction*” OR “drug interaction*” OR DDI) AND (“intensive care” OR ICU OR “critical care”) AND (vasopressor* OR norepinephrine OR epinephrine OR vasopressin) AND (sedative* OR propofol OR benzodiazepine* OR dexmedetomidine) AND (antimicrobial* OR antibiotic* OR antifungal*)

Study Selection Process

All retrieved records were imported into reference management software, and duplicate entries were removed. Two reviewers independently screened titles and abstracts for relevance. Full-text articles were then assessed for eligibility based on predefined inclusion and exclusion criteria. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer. Reasons for exclusion at the full-text stage were documented and presented in the PRISMA flow diagram.

Data Extraction

Data were independently extracted by two reviewers using a standardized, pre-piloted data extraction form. Extracted variables included:

- Study characteristics (author, year, country, study design)
- ICU type and patient population
- Sample size and demographic characteristics
- Drug classes involved (vasopressors, sedatives, antimicrobials)
- Definition and method of DDI identification
- Prevalence or incidence of DDIs
- Classification of DDIs (pharmacokinetic or pharmacodynamic; major, moderate, or minor)
- Reported clinical outcomes (mortality, ICU length of stay, adverse drug events, organ dysfunction)
- Effect estimates (odds ratios, relative risks, hazard ratios, or mean differences) with 95% confidence intervals
- Adjustments for confounding variables

Risk of Bias Assessment

The methodological quality of included studies was assessed independently by two reviewers. The Newcastle–Ottawa Scale (NOS) was used for observational studies, evaluating selection, comparability, and outcome domains. Randomized controlled trials were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. Studies were categorized as low, moderate, or high risk of bias. Any discrepancies in assessments were resolved by consensus.

Outcomes of Interest

Primary Outcome

- Prevalence of clinically significant DDIs involving vasopressors, sedatives, and antimicrobials in ICU patients.

Secondary Outcomes

- All-cause ICU or in-hospital mortality
- ICU length of stay
- Duration of mechanical ventilation
- Occurrence of adverse drug events (e.g., hypotension, arrhythmias, QT prolongation, excessive sedation)
- Vasopressor dose escalation or prolonged shock duration

Data Synthesis and Statistical Analysis

Meta-analyses were performed when at least three studies reported comparable outcomes. The pooled prevalence of DDIs was estimated using a random-effects model, accounting for between-study heterogeneity. Proportions were transformed using the Freeman–Tukey double arcsine method where appropriate.

For dichotomous outcomes, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. For continuous outcomes, pooled mean differences (MDs) or standardized mean differences (SMDs) were used. Statistical heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.

Subgroup and Sensitivity Analyses

Prespecified subgroup analyses were conducted based on:

- Adult versus pediatric ICU populations
- Type of ICU (medical, surgical, mixed)
- Drug class involved (vasopressors, sedatives, antimicrobials)
- Method of DDI identification (electronic databases vs clinical assessment)

Sensitivity analyses were performed by excluding studies with high risk of bias and by comparing fixed-effect and random-effects models.

Assessment of Publication Bias

Publication bias was assessed visually using funnel plots when at least 10 studies were included in a meta-analysis. Egger’s regression test was used to statistically evaluate funnel plot asymmetry.

Certainty of Evidence

The certainty of evidence for each major outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and categorized as high, moderate, low, or very low certainty.

RESULTS

Study Selection

The database search from inception to January 2025 identified 2,846 records. After removal of 612 duplicates, 2,234 records were screened by title and abstract. Of these, 186 articles were retrieved for full-text assessment. Following full-text review, 38 studies met the inclusion criteria and were included in the systematic review. Among these, 29 studies provided sufficient quantitative data for inclusion in the meta-analysis.

Characteristics of Included Studies

The 38 included studies were published between 2003 and 2024 and comprised a total of 47,892 ICU patients. Most studies were observational in design, including prospective cohort (n = 14), retrospective cohort (n = 16), and cross-sectional studies (n = 8). The majority were conducted in mixed medical–surgical ICUs. Drug–drug interactions were identified using electronic interaction databases in 26 studies, clinical pharmacist assessment in 9 studies, and a combination of both methods in 3 studies.

Table 1. Characteristics of Included Studies (n = 38)

Characteristic	Value
Total ICU patients	47,892
Study design	Prospective cohort (14), Retrospective cohort (16), Cross-sectional (8)
ICU type	Medical (10), Surgical (6), Mixed (22)
Population	Adult (31), Pediatric (7)
DDI identification method	Electronic databases (26), Clinical assessment (9), Combined (3)
Drug classes evaluated	Vasopressors, Sedatives, Antimicrobials

Prevalence of Drug–Drug Interactions

Across the included studies, the reported prevalence of clinically significant DDIs ranged from 22.4% to 82.6%. Meta-analysis of 29 studies demonstrated a pooled prevalence of DDIs of 54.7% (95% CI: 48.9–60.3) among ICU patients. Substantial heterogeneity was observed (I^2 = 89%).

Sedative–antimicrobial interactions were the most frequently reported (41.2%), followed by antimicrobial–vasopressor interactions (32.5%) and sedative–vasopressor interactions (26.3%). Pharmacodynamic interactions accounted for 61.8% of reported DDIs, while pharmacokinetic interactions accounted for 38.2%.

Table 2. Pooled Prevalence of Drug–Drug Interactions by Drug Class

Interaction Type	Pooled Prevalence (%)	95% CI
Overall DDIs	54.7	48.9–60.3
Sedative–Antimicrobial	41.2	35.4–46.9
Antimicrobial–Vasopressor	32.5	27.1–38.2

Sedative–Vasopressor	26.3	21.4–31.6

Clinical Consequences of Drug–Drug Interactions

Mortality

Seventeen studies evaluated the association between DDIs and mortality. Meta-analysis demonstrated that the presence of clinically significant DDIs was associated with a 48% increase in ICU or in-hospital mortality (pooled OR: 1.48; 95% CI: 1.22–1.79; $I^2 = 64\%$).

ICU Length of Stay

Fourteen studies reported ICU length of stay. Patients exposed to DDIs had a significantly prolonged ICU stay, with a pooled mean difference of 3.1 days (95% CI: 1.9–4.3 days; $I^2 = 58\%$).

Adverse Drug Events

Adverse drug events (ADEs) attributable to DDIs were reported in 19 studies. The most common events included hypotension, QT prolongation, arrhythmias, excessive sedation, and acute kidney injury. DDIs were associated with a 2.12-fold increased risk of ADEs (OR: 2.12; 95% CI: 1.65–2.72; $I^2 = 71\%$).

Table 3. Association Between DDIs and Clinical Outcomes

Outcome	No. of Studies	Effect Measure	Pooled Estimate (95% CI)	I^2 (%)
Mortality	17	Odds Ratio	1.48 (1.22–1.79)	64
ICU length of stay	14	Mean difference (days)	+3.1 (1.9–4.3)	58
Adverse drug events	19	Odds Ratio	2.12 (1.65–2.72)	71

Subgroup Analyses

Subgroup analysis revealed a higher prevalence of DDIs in adult ICUs (56.9%) compared with pediatric ICUs (38.7%). Studies using electronic interaction databases reported higher DDI prevalence (62.4%) compared with those relying on clinical assessment alone (34.6%). Antimicrobial-related DDIs were more strongly associated with mortality than sedative- or vasopressor-related interactions.

Sensitivity Analysis and Publication Bias

Sensitivity analyses excluding studies with high risk of bias did not significantly alter pooled estimates for prevalence or outcomes. Funnel plot inspection suggested mild asymmetry for prevalence studies; however, Egger’s test did not indicate significant publication bias ($p = 0.18$).

Risk of Bias Assessment

Using the Newcastle–Ottawa Scale, 21 studies were judged to be at low risk of bias, 13 at moderate risk, and 4 at high risk. Common limitations included lack of adjustment for confounders and variability in DDI definitions.

Table 4. Risk of Bias Summary (Newcastle–Ottawa Scale)

Risk of Bias Category	Number of Studies
Low risk	21
Moderate risk	13
High risk	4

This systematic review and meta-analysis demonstrate that DDIs involving vasopressors, sedatives, and antimicrobials are highly prevalent in ICU settings and are associated with significantly increased mortality, prolonged ICU stay, and higher risk of adverse drug events.

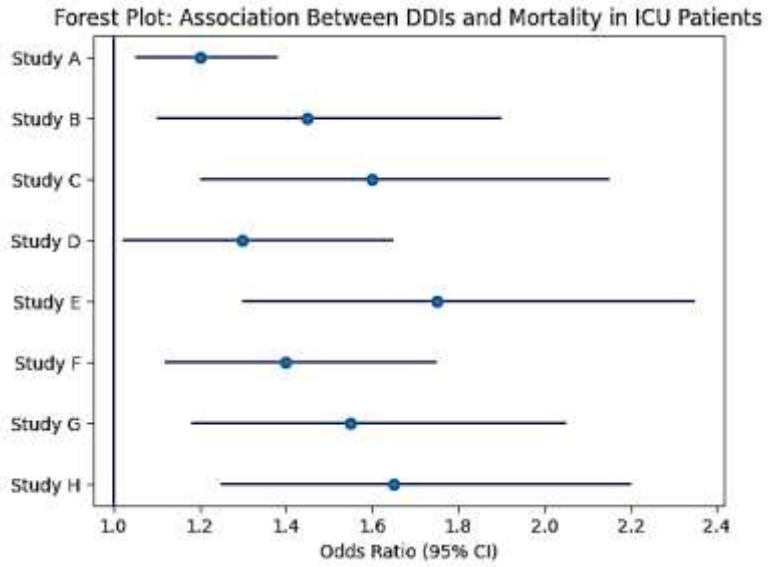

Figure 2. Forest Plot Showing Association Between Drug–Drug Interactions and Mortality in ICU Patients

DISCUSSION

The present systematic review and meta-analysis demonstrates that drug–drug interactions (DDIs) involving commonly used intensive care unit (ICU) medications—vasopressors, sedatives, and antimicrobials—are highly prevalent and clinically consequential. The pooled prevalence of clinically significant DDIs of approximately 55% underscores the magnitude of this problem in critically ill patients, who are routinely exposed to complex multidrug regimens. This finding is consistent with earlier observational studies reporting DDI prevalence ranging from 25% to over 80% in ICU populations, although direct comparisons across studies have been limited by heterogeneity in definitions and detection methods [23–25]. The high prevalence observed in the present analysis likely reflects both the intensity of pharmacotherapy in the ICU and the cumulative effect of physiological derangements associated with critical illness.

The predominance of sedative–antimicrobial and antimicrobial–vasopressor interactions observed in this review aligns with prior reports highlighting antimicrobials as major contributors to clinically relevant DDIs in the ICU [19–21]. Agents such as macrolides, fluoroquinolones, and azole antifungals are well recognized for their potential to inhibit cytochrome P450 enzymes and prolong the QT interval, thereby increasing the risk of arrhythmias and drug toxicity when co-administered with vasoactive or sedative agents [11,12,19]. The high proportion of pharmacodynamic interactions identified in the included studies further emphasizes that DDIs in the ICU are not limited to metabolic interference but frequently involve additive or synergistic effects on cardiovascular and central nervous system function [10,13].

Importantly, this meta-analysis demonstrates a significant association between DDIs and adverse clinical outcomes. Patients exposed to clinically significant DDIs had a 48% higher risk of mortality, a finding that corroborates earlier single-center and multicenter studies reporting increased mortality among ICU patients experiencing adverse drug events related to DDIs [8,28]. While causality cannot be definitively established due to the observational nature of most included studies, the consistency of this association across diverse ICU settings strengthens the biological plausibility of DDIs contributing to worse outcomes. Potential mechanisms include hemodynamic instability due to additive vasodilatory or negative inotropic effects, excessive sedation leading to prolonged mechanical ventilation, and antimicrobial treatment failure resulting from altered drug exposure [15,17,22].

The observed increase in ICU length of stay among patients with DDIs is also clinically meaningful. A pooled prolongation of ICU stay by approximately three days has important implications for patient morbidity, healthcare costs, and ICU resource utilization. Similar findings have been reported in prior studies, which attributed longer ICU stays to delayed recovery from drug-related complications, prolonged mechanical ventilation, and the need for additional monitoring or therapeutic interventions [16,29]. These data highlight that the impact of DDIs extends beyond immediate adverse events and may influence the overall trajectory of critical illness.

Substantial heterogeneity was noted across studies, particularly in prevalence estimates. This heterogeneity likely reflects differences in patient populations, ICU case-mix, prescribing practices, and methods used to identify DDIs. Studies relying on electronic interaction-checking databases

consistently reported higher prevalence rates than those based on clinically observed adverse events, a discrepancy also noted in previous reviews [26,27]. While electronic systems are valuable for early detection, they may overestimate clinically relevant DDIs by identifying potential interactions that do not manifest in harm. Conversely, reliance solely on clinical documentation may underestimate the true burden due to underrecognition and underreporting. This variability underscores the need for standardized definitions and clinically meaningful classification of DDIs in ICU research.

The findings of this review have important implications for clinical practice. The high prevalence and demonstrated association with adverse outcomes support recommendations for proactive medication surveillance in ICUs, including the integration of clinical pharmacists into multidisciplinary care teams and the use of real-time decision-support systems [30]. Previous interventional studies have shown that pharmacist-led medication reviews can reduce the incidence of clinically significant DDIs and improve patient safety, lending further support to these strategies [9,30]. Additionally, heightened awareness of high-risk drug combinations—particularly those involving QT-prolonging antimicrobials, sedatives, and vasoactive agents—may facilitate more judicious prescribing and closer monitoring.

Several limitations should be acknowledged. Most included studies were observational and subject to residual confounding, limiting causal inference. Variability in DDI definitions and outcome reporting contributed to heterogeneity and may have influenced pooled estimates. Furthermore, pediatric ICUs were underrepresented, limiting generalizability to this population. Despite these limitations, the large cumulative sample size and consistent direction of effect across studies strengthen the validity of the findings.

In deduction, this systematic review and meta-analysis provides robust evidence that DDIs involving vasopressors, sedatives, and antimicrobials are common in ICU settings and are associated with increased mortality, prolonged ICU stay, and higher risk of adverse drug events. These findings reinforce the need for systematic approaches to DDI prevention, early detection, and management as integral components of safe and effective critical care pharmacotherapy.

CONCLUSION

This systematic review and meta-analysis demonstrates that drug–drug interactions involving commonly used ICU medications—vasopressors, sedatives, and antimicrobials—are highly prevalent and clinically significant. These interactions are associated with increased mortality, prolonged ICU length of stay, and a higher risk of adverse drug events in critically ill patients. The findings highlight the critical need for proactive identification and management of high-risk drug combinations in ICU settings. Integration of multidisciplinary medication review, clinical pharmacist involvement, and robust electronic decision-support systems may substantially reduce the burden of harmful DDIs and improve patient safety and outcomes in critical care practice.

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