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Prevalence and clinical significance of potential drug-drug interactions of antimicrobials in Intensive Care Unit patients: a retrospective study

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Abstract

Background Antimicrobials are frequently prescribed in Intensive Care Units (ICUs), where drug-drug interactions (DDIs) with other medications may exacerbate clinical outcomes. Limited evidence exists on the prevalence and clinical impact of these interactions.

Objective To estimate the prevalence of potential DDIs (pDDIs) between antimicrobials and other drugs in ICU patients using two electronic DDIs databases, identify the actual DDIs and the most frequently implicated antimicrobials, and determine the risk factors associated with actual DDIs.

Methods We conducted a retrospective study on patients admitted to intensive care units from January to December 2023. Micromedex and Lexi-Interact were used to identify pDDIs and their severities. Furthermore, we used the Drug Interaction Probability Scale (DIPS) criteria to identify actual DDIs.

Results Among 2,154 patients, 2,163 pDDIs (108 unique pairs) were identified in 461 patients, and 2.87% (62 pDDIs in 46 patients) were classified as actual DDIs. The antimicrobials most likely to cause pDDIs included quinolones, triazole antifungals, and linezolid. Antimicrobial-drug pairs with a higher incidence of severe pDDIs included linezolid-dopamine/metoclopramide (hypertension), voriconazole-budesonide for inhalation (increased serum concentration of budesonide), and levofloxacin-amiodarone (QT prolongation). The antimicrobial-drug pairs with a higher occurrence of actual DDIs included linezolid-dopamine/dobutamine (hypertension), fluconazole-amiodarone/ritonavir (QT prolongation), and cefoperazone/vancomycin-furosemide (nephrotoxicity). Moderate agreement existed between the two databases for pDDIs detection (Cohen's kappa = 0.546), but severity ratings diverged. Multivariable analysis identified the number of drugs per patient (OR = 1.178, $p < 0.001$), the number of antimicrobials per patient (OR = 1.146, $p < 0.038$), and the length of stay in the ICU (OR = 1.093, $p < 0.038$) as significant risk factors.

Conclusions High pDDI rates involving antimicrobials were observed in ICU patients, though actual DDIs were infrequent. Notable severe risk pairs warrant vigilant monitoring, especially with a higher occurrence of actual DDIs. Discrepancies in DDI databases emphasize the need for multi-tool validation to optimize medication safety.

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Keywords Drug-drug interactions, Adverse drug reactions, Antimicrobials, Intensive Care Unit patients, Lexi-Interact, Micromedex

Introduction

Potential drug-drug interactions (pDDIs) may be defined as the concomitant administration of two or more interacting medications that could lead to a clinically relevant outcome [1]. It could increase the toxicity and reduce or increase the efficacy of a particular drug [2]. Due to polypharmacy, patients in the Intensive Care Unit (ICU) are at a greater risk for pDDIs. A systematic review revealed that 33% of general patients and 67% of ICU patients experienced a potential drug-drug interaction (pDDI) during their hospital stay [3]. Potential DDIs are the primary cause of preventable adverse drug reactions (ADRs) for this population [4, 5], causing higher mortality and morbidity, prolonged length of stay, and increased hospital costs [6]. A retrospective study found that the average length of stay for patients with drug-drug interactions (DDIs) was 15 days and 8 days for patients not exposed to DDIs [7]. Another study reported that the mortality in adult ICU patients with pDDIs was 66.7% [8]. Since pDDIs are primarily preventable, it is crucial to identify the pDDIs in a specific treatment environment, especially in the ICU.

Drug interaction programs are capable of identifying a substantial number of pDDIs; however, only a select few lead to clinically relevant adverse effects [9]. A systematic review has estimated that 58% of ICU patients encounter a pDDI, yet only a tiny fraction is deemed clinically significant [5]. One study conducted in the Surgical Intensive Care Unit reported that pDDIs were present in 38.9% of cases, with only 16.2% of those interactions being clinically relevant [10]. Another prospective study found that 89% of ICU patients exhibited at least one pDDI, but merely 8.46% of these interactions were considered clinically significant based on predetermined criteria [11]. A secondary analysis of a controlled pre-post study also found that 70.1% of hospitalized patients experienced a pDDI, but only 0.9% of patients with actual harm [12]. It is crucial to distinguish between potential and actual DDIs.

The incidence of drug interactions involving antimicrobials is increasing, as these agents are widely used among both inpatients and outpatients [13]. Research shows that seventy percent of patients in ICUs receive at least one antibiotic [14], which raises the possibility of antibiotic-drug and antibiotic-antibiotic interactions in this particular patient group. A comprehensive understanding of potential and actual DDIs between antimicrobials and other medications can assist intensive care physicians in making better medication choices and ultimately improving patient outcomes. However, evidence regarding these interactions is limited.

The primary objective of this study was to evaluate the occurrence and characteristics of potential and actual DDIs between antimicrobials and other drugs in ICU patients. Additionally, we aimed to assess the consistency of two databases used for rating DDIs.

Methods

Study design

We conducted a retrospective cross-sectional study at Beijing Tongren Hospital's three ICUs (Respiratory, Emergency, and Surgical), which have 30 beds. The study included all patients aged 18 years and older admitted to the ICUs and received at least two systemic medications (medications that are taken orally or by injection subcutaneously, inhalationally, intramuscularly, or intravenously), including at least one systemic antimicrobial, from January to December 2023. The institutional ethics committee of Beijing Tongren Hospital approved the research. Due to the study's retrospective and non-interventional nature, signed informed consent was not required.

Data collection and drug-drug interaction (DDI) identification

We used an Excel spreadsheet to collect patient information. Two pharmacists gathered patient demographics data, including age and gender, comorbidities, infection diagnoses, duration of ICU stay, and patient outcomes. They recorded a comprehensive medication profile that included all medications prescribed to each patient during their ICU stay, along with the start and end dates of these medications and the routes of administration. When gathering data, the two pharmacists entered the same dataset independently, followed by comparison to ensure accuracy and consistency. Differences in data entry were resolved through discussion or by consulting a third pharmacist.

We utilized the Lexi-Interact and Micromedex online databases to identify pDDIs between systemic antimicrobials and other long-term medications administered in the ICU. These databases have demonstrated the highest performance in detecting pDDIs, with superior detection sensitivity compared to other DDI screening programs [15, 16]. The two drug interaction checkers classify the severity of DDIs into several comparable categories but use different labels. For our analysis, we standardized the DDIs into five categories: severe, major, moderate, minor, and none (see Supplemental Table 1). DDIs classified as

Table 1 Demographic characteristics of adult prescriptions (n = 2154)

Patient characteristic	n (%) or median (IQR)
Age, median	61 (47.75, 72)
Gender	
Male	1,225 (56.87%)
Female	929 (43.13%)
ICU length of stay, days, median	15 (5, 16)
APACHE II score, median	11 (8, 17)
Comorbidity	
Cardiovascular diseases	1,077 (50%)
Endocrine disorders	558 (25.91%)
Pulmonary disease	788 (36.58%)
Chronic kidney diseases	311 (14.44%)
Nervous system diseases	265 (12.3%)
Immunodeficiency	124 (5.76%)
No. of prescribed drugs	27 (21, 32)
No. of prescribed antimicrobials	3 (2, 4)
Infection Site	
Pulmonary	1,196 (55.52%)
Intra-abdominal	557 (25.86%)
Perioperative prevention	223 (10.35%)
Skin or soft tissue	69 (3.2%)
Urinary tract	68 (3.16%)
Intracranial	41 (1.9%)

minor (no action needed) or none (no known interaction) were excluded from the analysis. Concurrent exposure to drugs was defined as administration within 24 hours, and switching one drug for another was not counted as co-administration. Additionally, we excluded 20 drugs that could not be searched in either interaction database from the study (see Supplemental Table 2).

To determine whether harmful pDDIs could lead to real clinical issues and thus become actual DDIs, both the pharmacist and the physician reviewed the medical records of all patients identified with pDDIs. This review included laboratory results and related signs and symptoms. Instances of laboratory test results and/or patient symptoms that confirmed clinically significant DDIs were noted. If the pharmacist and the physician reached a consensus on an adverse patient outcome, they utilized the Drug Interaction Probability Scale (DIPS) tool to evaluate the causality between a pDDI and an adverse drug reaction (ADR). The DIPS consists of 10 questions to assess the likelihood of a causal relationship between an observed event and the effects of a drug interaction [17]. The probability of a drug interaction is classified as doubtful (< 2), possible (2–4), probable (5–8), or highly probable (> 8). Interactions categorized as probable or highly probable were deemed actual DDIs.

Clinical decision guidelines and medical records defined or identified ADRs, such as nephrotoxicity, hyperglycemia, hypertension, cardiac arrhythmias, QT prolongation, angina, respiratory depression, nausea, vomiting, and seizures [18–22].

Statistical analyses

Data analyses were conducted using IBM SPSS® statistical software version 29.0. Categorical and continuous variables were described using either the mean ± standard deviation (SD) or the median (interquartile range [IQR)], depending on their distribution. Pearson's χ^2 test was employed to compare categorical variables. In contrast, continuous variables were compared using Student's t-tests for independent samples and the Mann-Whitney U test for non-normally distributed data. To evaluate the potential association between the occurrence of actual drug-drug interactions, both univariable and multivariable logistic regression analyses were performed to investigate risk factors associated with identified pDDIs. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each variable. The degree of agreement between the pDDIs identified by the two databases was assessed using the weighted Cohen's kappa test. Weighted kappa values were interpreted as follows: values ≤ 0 as indicating no agreement and 0 < values < 0.21 as poor, 0.21 ≤ values < 0.41 as fair, 0.41 ≤ values < 0.61 as moderate, 0.61 ≤ values < 0.81 as strong, and 0.81 ≤ values ≤ 1 as almost perfect agreement [23]. P values less than 0.05 were considered statistically significant.

Results

During the study period, 2,717 patients were admitted to the ICUs, and 2,154 patients who met the study's inclusion criteria were included for further analysis. The patient demographics are presented in Table 1. The median age was 61, and 56.87% were male. The patients were prescribed and administered a median of 27 drugs from various categories. Most patients stayed between 5 and 16 days in the ICU, with a median stay of 15 days. The patient severity, measured using the APACHE II score, was 11, with an interquartile range of 8–17. The most common comorbidities were cardiovascular diseases, such as hypertension, hyperlipidemia, and coronary heart disease. The infection sites included pulmonary, intra-abdominal, perioperative prevention, skin or soft tissue, urinary tract, and intracranial. Most medications were administered intravenously (82.36%). The overall ICU medication categories were analyzed according to AHFS Drug Information® 2023, and the results (% of total prescriptions) were displayed in Fig. 1. The top three most prescribed medication categories were anti-infective agents (25.12%), central nervous system agents (16.74%), and electrolyte, caloric and water balance agents (13.58%). Most antimicrobials were also administered intravenously (92.1%). The average number of antimicrobials prescribed for every patient ranged from

Table 2 Potential DDIs with severe category risk according to severity indicated by Micromedex and Lexi-Interact

Antimicrobials	Other drug	n	Lexi-Interact	Micromedex	Potential clinical consequence
Linezolid	Dopamine	25	None	Contraindicated	Increased hypertensive effects
Voriconazole	Budesonide for inhalation	15	X-Moderate	None	Increased serum concentration of budesonide
Linezolid	Metoclopramide	7	X-Moderate	None	Increased hypertensive effect of linezolid
Levofloxacin	Amiodarone	5	X-Major	None	Increased QT prolongation of amiodarone
Linezolid	Tramadol	4	None	Contraindicated	Increased risk of serotonin syndrome or opioid toxicity and seizures
Linezolid	Epinephrine	4	None	Contraindicated	Increased hypertensive effects
Moxifloxacin	Amiodarone	4	X-Major	None	Increased QT prolongation of moxifloxacin
Linezolid	Morphine	4	X-Moderate	None	Increased adverse/toxic effect of morphine (systemic)
Linezolid	Dobutamine	4	D-Moderate	Contraindicated	Increased hypertensive effects
Fluconazole	Ritonavir	3	None	Contraindicated	Increased ritonavir exposure and an increased risk of QT prolongation
Voriconazole	Amiodarone	3	X-Major	None	Increased QT prolongation of voriconazole and Increased serum concentration of amiodarone
Fluconazole	Amiodarone	3	D-Major	Contraindicated	Increased QT prolongation and serum concentration of amiodarone
Linezolid	Pethidine	2	None	Contraindicated	Increased risk of serotonin syndrome or opioid toxicity
Fluconazole	Ondansetron	2	None	Contraindicated	increased ondansetron exposure and an increased risk of QT prolongation
Linezolid	Pseudoephedrine	2	None	Contraindicated	Hypertensive crisis (headache, hyperpyrexia, hypertension)
Amikacin	Mannitol	2	X-Major	None	Increased Nephrotoxic effect of aminoglycosides
Levofloxacin	Domperidone	2	X-Moderate	Major	Increased QT prolongation of domperidone
Voriconazole	Papaverine	2	X-Major	None	Increased QT prolongation of voriconazole and Increased serum concentration of papaverine
Voriconazole	Ivabradine	1	X-Moderate	Contraindicated	Increased exposure of ivabradine and increased risk of QT prolongation
Fluconazole	Domperidone	1	X-Major	Contraindicated	Increased domperidone exposure and an increased risk of QT prolongation
Voriconazole	Ritonavir	1	None	Contraindicated	Decreased plasma concentrations of voriconazole with high-dose and, to a lesser extent, low-dose ritonavir, and risk of reduced voriconazole efficacy
Voriconazole	Domperidone	1	X-Major	None	Increased QT prolongation and serum concentration of domperidone

2 to 4, with a median of 3 drugs per patient. Among all the anti-infective agents, meropenem was the most prescribed drug, followed by cefperazone-sulbactam and vancomycin (Fig. 2).

A total of 2163 pDDIs were identified between systemic antimicrobials and other drugs using the two drug interaction databases, involving 108 different drug interaction pairs. Twenty-one point four percent of patients (461/2154) experienced at least one pDDI during their ICU stay, corresponding to 1.9 per patient. Lexi-Interact identified 1052 pDDIs with 101 different pairs. Based on the severity categories, these pDDIs were categorized as follows: minor (38/1052, 3.61%), moderate (834/1052, 79.28%), major (133/1052, 12.64%), and severe (47/1052, 4.47%) (Fig. 1). A total of 1111 pDDIs were identified by the Micromedex with 97 different pairs, of which 77(6.93%), 982 (88.39%), and 52 (4.68%) pDDIs were rated with the severity categories of moderate, major, and contraindicated respectively (Fig. 3). The potential clinical consequences with related interaction mechanisms for the top 20 pDDIs are shown in Supplemental Table 3. Severe pDDIs accounted for 4.48% (97/2163). Details of the severe types of pDDIs are shown in Table 2.

An inter-rater reliability analysis was performed between Lexi-Interact and Micromedex, and the overall Cohen's Kappa is 0.546 with a p-value (p) < 0.001, which means moderate agreement between the two databases. The kappa values were – 0.726, – 0.011, and 0.147 for the interaction pairs of severe, major, and moderate categories separately, and there was no agreement between the two databases.

Actual DDIs between systemic antimicrobials and other drugs

Of all the 2,163 pDDIs, 62 actual DDIs (2.87%) led to ADRs in 46 patients, with seven of these patients (1.52%) requiring emergency treatment. According to the DIPS

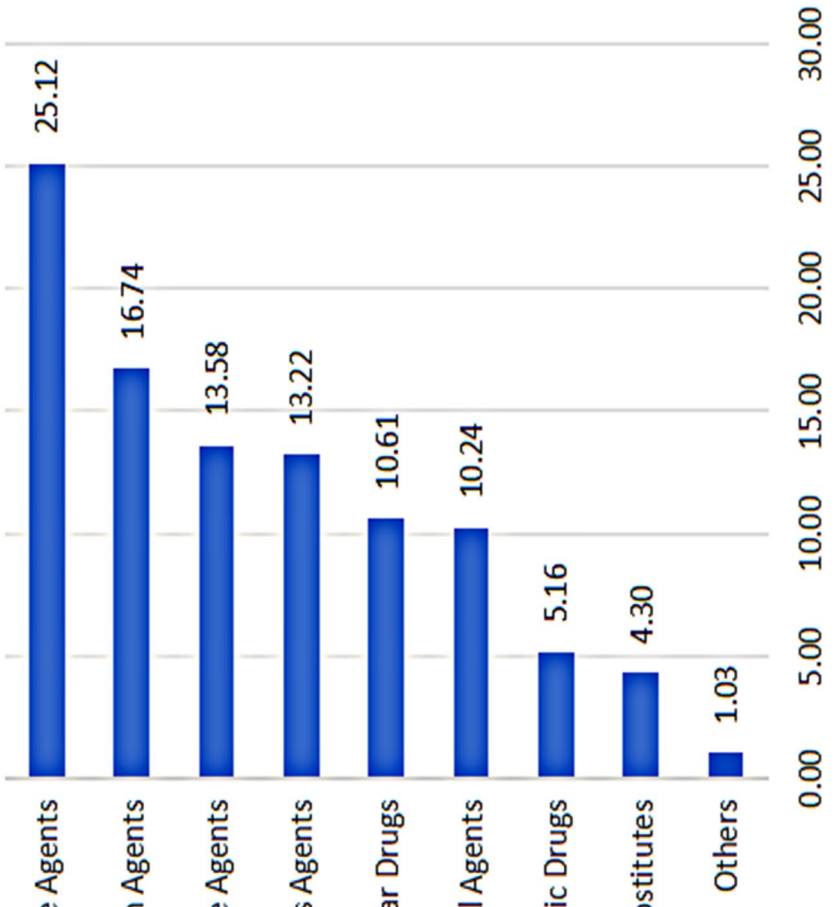

Fig. 1 Categories of ICU medication utilization (% total prescriptions)

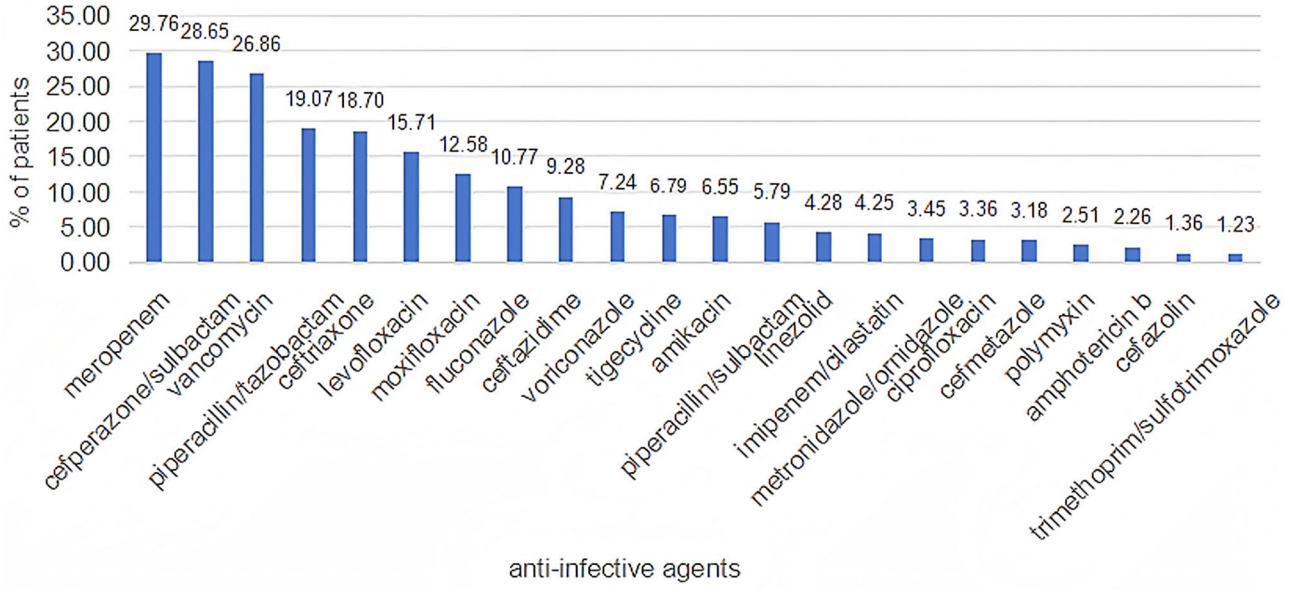

Fig. 2 Percent of patients receiving different anti-infective agents

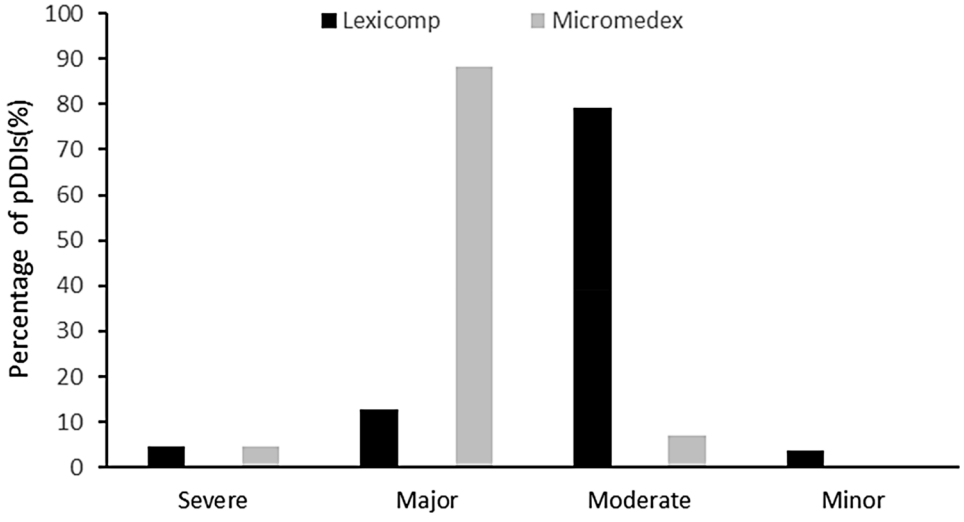

Fig. 3 Severity of risk rating of pDDIs (minor, moderate, major, and severe) by Micromedex and Lexi-Interact

criteria, 29 actual DDIs were classified as possible, while 33 were deemed probable (see Table 3).

Among the 1,052 pDDIs identified by Lexi-Interact, only 52 (4.94%) were confirmed as actual DDIs, with 24 classified as possible and 28 as probable according to the DIPS criteria. Similarly, from 1,111 pDDIs identified by Micromedex, 55 (4.95%) resulted in actual DDIs, consisting of 31 possible and 24 probable classifications based on the DIPS criteria. A total of 10 different antimicrobials were involved in the actual DDIs. Linezolid and levofloxacin were most frequently implicated, with 18 and 11 actual DDIs, respectively. Of the three pDDIs involving the fluconazole-amiodarone combination, two (66.67%) were classified as actual DDIs. In the case of the two pDDIs involving fluconazole-Ondansetron, both (100%) were actual DDIs. Of the four pDDIs involving the linezolid-epiephrine combination, two (50%) were actual DDIs. According to Lexi-Interact or Micronmedex, all the actual DDIs mentioned above were rated as having a severity of D or considered contraindicated. Out of the 62 actual DDIs, 48 were classified as having a major severity or were contraindicated. The most common clinical manifestations of ADRs related to actual DDIs included QT prolongation, nephrotoxicity, hypoglycemia, hypertension, and bleeding.

Among the 62 actual DDIs identified, seven patients (1.52%) experienced emergencies. The remaining 39 patients presented only with mild clinical issues such as

Table 3 Adverse drug reactions caused by actual drug-drug interactions and management of the toxicities

DDI-related ADRs	pDDIs pairs	Lexi-Interact	Micromedex	Number of actual DDI	Actual DDI DIPS score	Time to develop ADRs after drug combination, (days)	Management
Hypoglycemia	Linezolid-Insulin	C-Moderate	Moderate	5	3, 3, 4, 4, 4	6.2 ± 0.75	Adjust insulin/hypoglycemic agent dose, and monitor blood glucose
	Levofloxacin-Hypoglycemic agent	C-Moderate	Major	4	3, 3, 5, 5	4.25 ± 0.83	
Nephrotoxicity	Cefoperazone-Furosemide	C-Moderate	Major	4	4, 5, 5, 6	6 ± 1.58	Adjust dose of cephalosporins, monitor renal function
	Vancomycin-Loop Diuretics	C-Moderate	None	3	5, 6, 7	3.67 ± 0.47	Discontinue vancomycin or Change it to linezolid
	Vancomycin-Piperacillin/Tazobactam	C-Moderate	Major	3	4, 6, 7	5.67 ± 2.05	
	Levofloxacin-NSAIDs*	C-Major	Moderate	1	6	6	Change quinolones to other antibiotics
	Amikacin-Vancomycin	D-Moderate	Major	1	8	4	Change vancomycin or amikacin to other antibiotics
	Amikacin-Torsemide	C-Moderate	Moderate	1	6	5	
	Amikacin-Furosemide	C-Moderate	Moderate	2	7, 7	5.5 ± 0.5	
Hypertension	Linezolid-Dopamine	D-Major	Contraindicated	2	5, 5	7.5 ± 0.5	Add antihypertensive drugs and monitor blood pressure
	Linezolid-Noradrenaline	D-Moderate	Major	2	5, 5	4.5 ± 0.5	
	Linezolid-Aminophylline	D-Moderate	none	2	2, 3	6.5 ± 0.5	
	Linezolid-Metoclopramide	X-Moderate	None	1	2	6	
	Linezolid-Epinephrine	None	Contraindicated	2	3, 4	4.5 ± 0.5	
QT prolongation	Linezolid-Ondansetron	C-Moderate	Major	3	3, 4, 4	5.33 ± 1.25	Monitor clinical symptoms and change or discontinue related medications as needed
	Levofloxacin-Ondansetron	C-Moderate	Major	3	3, 4, 4	4.33 ± 1.25	
	Fluconazole-Amiodarone	D-Major	Contraindicated	2	6, 6	7 ± 1	
	Fluconazole-Ondansetron	None	Contraindicated	2	3, 4	7 ± 2	
	Levofloxacin-Famotidine	None	Major	2	5, 6	8.5 ± 1.5	
	Levofloxacin-Amiodarone	X-Major	None	1	7	4	
	Voriconazole-Propofol	C-Moderate	None	1	6	7	
	Metronidazole-Famotidine	None	Major	1	4	6	
Bleeding	Cefoperazone-Heparin	None	Major	4	3, 3, 3, 4	4 ± 1.22	Adjust the dose of anticoagulant drugs to monitor coagulation function and bleeding
	Fluconazole-Rivaroxaban	C-Major	Moderate	1	5	11	
Cardiac arrhythmias	Metronidazole-Dexmedetomidine	None	Major	1	5	9	Discontinue metronidazole
Angina	Fluconazole-Clopidogrel	D-Major	Major	1	3	6	Change fluconazole to voriconazole
Nausea, vomiting	Ciprofloxacin-Aminophylline	D-Major	None	3	5, 6, 6	5.67 ± 1.25	Add antiemetics
	Imipenem-Theophylline	None	Major	1	4	3	
Seizures	Voriconazole-Tramadol	C-Moderate	Major	1	3	5	Change tramadol to flurbiprofen

Table 3 (continued)

DDI-related ADRs	pDDIs pairs	Lexi-Interact	Micromedex	Number of actual DDI	Actual DDI DIPS score	Time to develop ADRs after drug combination, (days)	Management
Serotonin syndrome	Linezolid-Morphine	X-Moderate	None	1	6	4	Change linezolid to vancomycin
Respiratory depression	Voriconazole-Sufentanil	C-Moderate	Major	1	3	3	Discontinue sufentanil

*NSAIDs: Nonsteroidal Anti-Inflammatory Agent

electrolyte disturbances, bleeding, vomiting, hypertension, or elevated creatinine levels. No life-threatening DDIs were observed in this study.

Risk factors associated with actual DDIs in ICU patients

The results of the univariable and multivariate logistic regression analysis models used to analyze the risk factors associated with actual DDIs are shown in Table 4 and Table 5. Univariable analysis showed a statistically significant correlation between the ICU length of stay ($p = 0.047$), number of drugs per patient ($p < 0.001$), and number of antimicrobials per patient ($p < 0.001$). There was no significant relationship with age, gender, comorbidity, infection site, or number of pDDIs per patient. Multivariable logistic regression analyses showed that the number of drugs per patient (OR, 1.178; 95% CI, 1.129–1.218; $p < 0.001$), number of antimicrobials per patient (OR, 1.146; 95% CI, 1.075–1.217; $p < 0.038$), and ICU length of stay (OR, 1.093; 95% CI, 1.061–1.128; $p < 0.038$) were statistically significantly to predict actual DDIs.

Discussion

Patients in the ICU are particularly vulnerable to DDIs due to the extensive use of multiple medications and the complex nature of their treatments. Antimicrobials are among the most commonly prescribed drugs, as infectious diseases are frequently encountered in this population. Physicians and pharmacists must identify and assess the risks associated with antibiotic-drug and antibiotic-antibiotic interactions in ICU patients. This study represents the first effort to evaluate the prevalence of pDDIs among ICU patients receiving antimicrobials and to assess the clinically relevant DDIs that may arise.

The retrospective data-based study revealed that over one-fifth of ICU patients receiving antimicrobial medications experienced at least one pDDI with other treatments. However, among the 461 patients identified with pDDIs, only 46 exhibited actual drug-drug interactions that could lead to clinically significant ADRs. Previous research indicated that pDDI rates in ICU populations ranged from 54% to 94.7%, depending on the database used [11, 14, 24–28]. Additionally, Sulaiman et al. reported DDI rates between antimicrobials and other prescribed medications to be 21.74% and 16.43% in community and outpatient settings, respectively, when utilizing Google Bard and Lexi-Interact [29]. Another investigation involving renal transplant recipients found percentages of clinically relevant DDIs to be 4.0%, 4.2%, and 8.2%, based on three different interaction checker programs [30]. While comparing the prevalence of DDIs presents challenges due to variations in study populations, designs, DDI criteria, and screening databases, the prevalence observed in this study aligns with earlier findings. Our results further confirm the high rate of pDDIs

Table 4 Logistic regression analysis for risk factors associated with actual drug-drug interactions in ICU patients

Variable	With actual DDIs (n = 46)	Without actual DDIs (n = 415)	*p*
Age,years	72 (50, 77.5)	57.5 (44, 70)	0.135
Age, ≧65	20 (43.48%)	157 (37.83%)	0.447
Gender, male(%)	25 (54.35%)	209 (50.36%)	0.597
ICU length of stay, days	16.75 (5.25, 21)	14 (5, 14.5)	0.047
APACHE II score	17.5 (12.25, 21)	15 (15, 22)	0.466
Comorbidity			
Cardiovascular diseases	29 (63.04%)	223 (53.73%)	0.223
Endocrine disorders	15 (32.61%)	122 (29.4%)	0.644
Pulmonary disease	18 (39.13%)	159 (38.31%)	0.904
Chronic kidney diseases	7 (15.21%)	56 (13.49%)	0.742
Nervous system diseases	7 (15.21%)	53 (12.77%)	0.635
Immunodeficiency	4 (8.7%)	22 (5.3%)	0.341
Infection Site			
Pulmonary	26 (56.52%)	255 (61.45%)	0.529
Intra-abdominal	11 (23.91%)	101 (24.34%)	0.956
Perioperative prevention	6 (13.04%)	43 (10.36%)	0.572
Skin or soft tissue	2 (4.35%)	19 (4.58%)	0.946
Urinary tract	3 (6.52%)	17 (4.1%)	0.451
Intracranial	1 (2.17%)	8 (1.93%)	0.907
No. of prescribed drugs per patient	38 (27, 39)	32 (20, 33.5)	< 0.001
No. of antimicrobials per patient	6 (5, 8)	3 (2, 6)	< 0.001
No. of pDDIs per patient	2 (2, 3)	2 (1, 2)	0.057

specifically involving antimicrobials and other drugs in critically ill patients; however, the occurrence of actual DDIs leading to clinically relevant ADRs was infrequent.

Due to the absence of a single DDI database with 100% sensitivity or specificity for evaluating DDIs [31], along with inconsistencies in severity grading and the inclusion of pDDIs among existing databases [32], we categorized the DDI pairs based on two major databases: Micromedex and Lexi-Interact. In our analysis, Micromedex and Lexi-Interact identified comparable pDDIs (1111 vs. 1055). The two databases demonstrated moderate agreement in identifying pDDIs between antimicrobials and other medications, with a kappa value of 0.546. Variations between the databases are likely due to differences in the underlying databases, algorithms, and data sources. Notably, no prior studies have examined the consistency of these databases in identifying pDDIs between antimicrobials and other drugs in ICU patients. Research conducted in other populations or with different medications has shown similar levels of agreement (fair or moderate) between the two databases [33–37].

Lexi-Interact classified 5.99% of pDDIs as severe, 30.41% as major, and 59.41% as moderate in severity. In contrast, Micromedex classified 4.68%, 88.39%, and 6.93% of pDDIs as severe, major, and moderate. This indicates that Lexi-Interact tends to categorize many interactions as moderate severity, whereas Micromedex categorizes a higher proportion as major severity. Furthermore, the severity ratings of pDDIs between the two databases exhibited low agreement. Specifically, there was no agreement for severe and major pDDIs (kappa = – 0.726 and – 0.011, respectively) and only poor agreement for moderate pDDIs (kappa = 0.147). These severity rating discrepancies align with previous studies' findings [30, 34]. The differences in the categorization of moderate and major severity pDDIs between Lexi-Interact and Micromedex may be addressed in practice since most of the pDDIs warrant monitoring.

Our study identified the five most common pDDIs among the following pairs of drug classes: cefoperazone and heparin, vancomycin and piperacillin-tazobactam, quinolones and blood glucose lowering agents, quinolones and corticosteroids, and vancomycin and loop diuretics. The antimicrobials most likely to cause pDDIs included quinolones, triazole antifungals, and linezolid. Notably, linezolid was associated with the highest incidence of pDDIs categorized as "X" or "Contraindicated." A cross-sectional study revealed that 67.9% of patients experienced pDDIs with linezolid, with 20.8% of patients receiving contraindicated concomitant medications [38]. Particular attention should be given to drug-drug interactions in ICU patients treated with linezolid. These interactions' most common clinical consequences included QT prolongation, bleeding, and nephrotoxicity, findings that align with those from many previous studies [39–42].

Numerous studies have assessed various DDI screening systems, yet few have concentrated on the prevalence of actual DDIs that could result in clinically significant ADRs. An actual DDI is defined by patient outcomes rather than merely the presence of pDDIs in drug interaction programs. Our research indicated that a relatively small proportion of identified pDDIs turned out to be actual DDIs, particularly among those classified with

Table 5 Univariable and multivariable logistic regression analysis for independent risk factors for actual drug-drug interactions in ICU patients

Risk factor	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
ICU length of stay, days	1.097 (1.064–1.135)	0.049	1.093 (1.061–1.128)	0.038
No. of prescribed drugs per patient	1.187 (1.134–1.221)	< 0.001	1.178 (1.129–1.218)	< 0.001
No. of antimicrobials per patient	1.169 (1.09–1.235)	< 0.001	1.146 (1.075–1.217)	< 0.001

moderate severity by Micromedex and Lexi-Interact ratings. The majority of actual DDIs were categorized as major or severe, but most patients experienced only mild clinical consequences, with none facing life-threatening situations. Muhič et al. reported that the rate of probable clinically relevant DDI-related ADRs in patients urgently admitted to medical departments is 3.7% [43]. Souza et al. reported that actual DDIs occurred in 3.6% of patients [44]. Similarly, Becker et al. found that DDIs accounted for 0.6% of all hospital admissions [45]. Our findings align with those of these studies. We also observed that the total number of medications and antimicrobials administered per patient, along with the length of ICU stay, was associated with an increased risk of actual DDIs. This result corroborates earlier research. For instance, Gago-Sánchez et al. identified that the number of prescribed drugs, as well as the prescription of tacrolimus, was linked to a heightened risk of real DDIs in transplant patients [46].

Furthermore, Zhang et al. found a correlation between the number of co-administered drugs and an increased risk of category X drug interactions [47]. A separate study involving cancer patients noted a significant association between pDDIs and the duration of hospital stay [48]. We did not identify other risk factors that showed a substantial correlation with pDDIs, such as age, gender, comorbidity, infection site, or the number of pDDIs per patient. However, a study conducted in a cardiothoracic ICU highlighted a strong relationship between pDDIs and age [49]. The discrepancies observed across various studies may be attributed to differences in selected populations, medications, and other factors.

This study has several limitations. Firstly, it was an uncontrolled, retrospective analysis with a small sample size. Some ADRs may not have been documented in the medical records, potentially introducing bias into the results. Secondly, our focus was limited to the screening of DDIs between antimicrobials and other prescribed medications, which does not fully capture the overall clinical significance of pDDIs in ICU patients. Additionally, it was often challenging to determine whether the observed ADRs were attributable to the DDIs we identified, other DDIs, or simply a single medication. The complexity increased when attempting to distinguish if the pDDIs were the result of interactions between pairs of drugs or multiple interactions involving three or more drugs. Thirdly, we did not account for the half-lives of the medications, which may have led to an overestimation or underestimation of pDDIs based on the duration of action of the involved drugs. Fourth, information on medications not approved by the US FDA was limited, as they were not included in the two DDI databases utilized. Finally, we employed DIPS to assess drug interaction causality and evaluate DDI-related ADRs; however, this approach heavily relies on the knowledge and information available to the individual, which may introduce significant inter-individual variability.

Conclusions

Our study showed that pDDIs between antimicrobials and other drugs frequently occur in ICU patients. However, the incidence of actual DDIs remains relatively small, and the related clinical consequences are generally harmless. The discrepancies between Micromedex and Lexi-Interact in severity classification underscore the necessity of using multiple DDI databases to evaluate clinical pDDIs, considering unique patient characteristics and clinical situations. Considering the continuous emergence of bacteria resistance and the emergence of new antibiotics, further trials would also be required to assess the interactions between new antibiotics and other drugs. Our findings emphasize the importance of targeted monitoring for high-risk antimicrobial combinations. Automated alerts for high-risk pDDIs in electronic health records and multidisciplinary team reviews of antimicrobial regimens could reduce avoidable harm. Future interventions should prioritize real-time therapeutic drug monitoring (e.g., voriconazole trough levels) and protocol-driven surveillance for interactions involving QT-prolonging agents or nephrotoxic combinations (e.g., vancomycin-piperacillin/tazobactam).

Supplementary information

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Supplementary Material 1

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Author contributions

S.X. contributed to the study design, methodology, data collection and examination, data analysis and manuscript drafting. Z.S. and J.B. contributed to data extraction and examination. J.W. made critical revisions. All authors have reviewed and approved the final manuscript.

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Data availability

The datasets used and/or analyzed in the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The protocols used in this retrospective study were reviewed and approved by the institutional ethics board of Beijing Tongren Hospital (TRECKY2024-106). The requirement for individual informed consent was waived by the institutional ethics board of Beijing Tongren Hospital because this study used currently existing medical records collected during the course of routine medical care and did not pose any additional risks to the patients. All patient

data were anonymized prior to the analysis. All methods and experimental protocols in this study were conducted in accordance with the approved protocols and Ethics Committee's existing guidelines.

Consent for publication
Not applicable.

Principal investigator statement
The authors confirm that the Principal Investigator for this paper is Shanshan Xu and that she had direct clinical responsibility for patients.

Competing interests
The authors declare that they have no competing interests.

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References

1. Uijtendaal EV, van Harssel LL, Hugenholtz GW, et al. Analysis of potential drug-drug interactions in medical intensive care unit patients. Pharmacotherapy 2014;34:213–19.
2. Holm J, Eiermann B, Eliasson E, et al. A limited number of prescribed drugs account for the great majority of drug-drug interactions. Eur J Clin Pharmacol 2014;70:1375–83.
3. Zheng WY, Richardson LC, Li L, et al. Drug-drug interactions and their harmful effects in hospitalised patients: a systematic review and meta-analysis. Eur J Clin Pharmacol 2018;74:15–27.
4. Rivkin A.Admissions to a medical intensive care unit related to adverse drug reactions. Am J Health Syst Pharm. 2007;64(17):1840–43.
5. Fitzmaurice MG, Wong A, Akerberg H, et al. Evaluation of potential drug-drug interactions in adults in the intensive care unit: a systematic review and meta-analysis. Drug Saf 2019;42:1035–44.
6. Kane-Gill SL, Dasta JF, Buckley MS, et al. Clinical Practice Guideline: safe Medication Use in the ICU. Crit Care Med 2017;45:e877–e915.
7. Moura CS, Acurcio FA, Belo NO.Drug-drug interactions associated with length of stay and cost of hospitalization. J Pharm Pharm Sci. 2009;12(3):266–72.
8. Aşcı H, Sönmez Y, Saygın M, et al. Investigation of the presence of potential drug-drug interactions in the adult intensive care unit: a retrospective study. Süleyman Demirel Üniversitesi Tip Fakültesi Dergisi 2016;23:87–96.
9. Leal Rodríguez C, S. K-HB, et al. Drug interactions in hospital prescriptions in Denmark: prevalence and associations with adverse outcomes. Pharmacoepidemiol Drug Saf 2022;31:632–42.
10. Shakeel F, Khan JA, Aamir M.Relationship of factors affecting clinically important drug interactions and their significance in surgical intensive care units in Pakistan. Lat Am J Pharm. 2018;37(4):643–50.
11. Hasan SS, Lim KN, Anwar M, et al. Impact of pharmacists' intervention on identification and management of drug-drug interactions in an intensive care setting. Singap Med J 2012;53:526–31.
12. Li L, Baker J, Quirk R, et al. Drug-Drug Interactions and Actual Harm to Hospitalized Patients: a Multicentre Study Examining the Prevalence Pre- and Post-Electronic Medication System Implementation. Drug Saf 2024;47:557–69.
13. Pai MP, Momary KM, Rodvold KA. Antibiotic drug interactions. Med Clin North Am. 2006;90:1223–55.
14. Vincent JL, Sakr Y, Singer M, et al. Prevalence and Outcomes of Infection among Patients in Intensive Care Units in 2017. Jama 2020;323:1478–87.
15. Kheshti R, Aalipour M, Namazi S.A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. J Res Pharm Pract. 2016;5(4):257–63.
16. Clauson KA, Marsh WA, Polen HH, et al. Clinical decision support tools: analysis of online drug information databases. BMC Med Inform Decis Mak. 2007;7:7.
17. Horn JR, Hansten PD, Chan L-N.Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother. 2007;41(4):674–80.
18. Khwaja A.KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179–c184.
19. American Diabetes Association Professional Practice Committee. Glycemic Goals and Hypoglycemia: standards of Care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1).
20. Mancia G, Kreutz R, Brunström M, et al. ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens 2023;41:1874–2071.
21. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43(40):3997–4126.
22. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. Part iv: the ST segment, T and U waves, and the QT interval. A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Co. J Am Coll Cardiol. 2009;53:982–91.
23. McHugh ML.Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276–82.
24. Lima REF, De Bortoli Cassiani SH.Potential drug interactions in intensive care patients at a teaching hospital. Rev Lat Am Enfermagem. 2009;17(2):222–27.
25. Ismail M, Khan F, Noor S, et al. Potential drug-drug interactions in medical intensive care unit of a tertiary care hospital in Pakistan. Int J Clin Pharm 2016;38:1052–56.
26. Reis AMM, Cassiani SHDB.Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. Clinics (Sao Paulo). 2011;66(1):9–15.
27. Vanham D, Spinewine A, Hantson P, et al. Drug-drug interactions in the intensive care unit: do they really matter? J Crit Care. 2017;38:97–103.
28. Jafarova Demirkapu M, Pinar Kara S.Potential drug-drug interactions in University Hospital Medical Intensive Care Unit patients in Turkey. Eur Rev Med Pharmacol Sci. 2021;25(22):7108–14.
29. Sulaiman DM, Shaba SS, Almufty HB, et al. Screening the Drug-Drug Interactions Between antimicrobials and Other Prescribed Medications Using Google Bard and Lexicomp® Online™ Database. Cureus 2023;15:e44961.
30. Tecen-Yucel K, Bayraktar-Ekincioglu A, Yildirim T, et al. Assessment of Clinically Relevant Drug Interactions by Online Programs in Renal Transplant Recipients. J Manag Care Spec Pharm 2020;26:1291–96.
31. Rogala BG, Charpentier MM, Nguyen MK, et al. Oral anticancer therapy: management of drug interactions. J Oncol Pract 2019;15:81–90.
32. Benoist GE, van Oort IM, Smeenk S, et al. Drug-drug interaction potential in men treated with enzalutamide: mind the gap. Br J Clin Pharmacol 2018;84:122–29.
33. Liu Y, Wang J, Gong H, et al. Prevalence and associated factors of drug-drug interactions in elderly outpatients in a tertiary care hospital: a cross-sectional study based on three databases. Ann Transl Med 2023;11:17.
34. Abbas A, Al-Shaibi S, Sankaralingam S, Awaisu A, et al. Determination of potential drug-drug interactions in prescription orders dispensed in a community pharmacy setting using Micromedex® and Lexicomp®: a retrospective observational study. Int J Clin Pharm 2022;44:348–56.
35. Bektay MY, Seker Z, Eke HK, et al. Comparison of different decision support software programs in perspective of potential drug-drug interactions in the oncology clinic. J Oncol Pharm Pract 2023;29:1178–86.
36. Bossaer JB, Thomas CM.Drug Interaction Database Sensitivity With Oral Antineoplastics: an Exploratory Analysis. J Oncol Pract. 2017;13(3):e217–22.
37. Roca B, Roca M. Assessment of Drug Interactions with Online Electronic Checkers in Multi-Pathological Patients. Pharmacology. 2022;107:111–15.
38. Jiang HY, Yu LY, Wang X, et al. Prevalence of potential drug-drug interactions among intensive care unit patients receiving linezolid: a cross-sectional study. Eur Rev Med Pharmacol Sci 2023;27:9396–400.
39. Armahizer MJ, Seybert AL, Smithburger PL, Kane-Gill SL. Drug-drug interactions contributing to QT prolongation in cardiac intensive care units. J Crit Care. 2013;28:3):243–9.
40. Edrees H, Amato MG, Wong A, et al. High-priority drug-drug interaction clinical decision support overrides in a newly implemented commercial computerized provider order-entry system: override appropriateness and adverse drug events. J Am Med Inform Assoc. 2020;27:6):893–900.
41. Reis AM, Cassiani SH.Adverse drug events in an intensive care unit of a university hospital. Eur J Clin Pharmacol. 2011;67(6):625–32.
42. Bakker T, Abu-Hanna A, Dongelmans DA, et al. Clinically relevant potential drug-drug interactions in intensive care patients: a large retrospective observational multicenter study. J Crit Care. 2021;62:124–30.

43. Muhič N, Mrhar A, Brvar M.Comparative analysis of three drug-drug interaction screening systems against probable clinically relevant drug-drug interactions: a prospective cohort study. Eur J Clin Pharmacol. 2017;73(7):875–82.
44. Cruciol-Souza J, Thomson JC. A pharmacoepidemiologic study of drug interactions in a Brazilian teaching hospital. Clinics. 2006;61:515–20.
45. Becker ML, Kallewaard M, Caspers PWJ, et al. Hospitalisations and emergency department visits due to drug-drug interactions: a literature review. Pharmacoepidemiol Drug Saf. 2007;16:641–51.
46. Gago-Sánchez AI, Font P, Cárdenas M, et al. Real clinical impact of drug-drug interactions of immunosuppressants in transplant patients. Pharmacol Res Perspect. 2021;9(6).
47. Zhang J, Ma D, Chen M, et al. Prevalence and clinical significance of potential drug-drug interactions among lung transplant patients. Front Pharmacol. 2024;15:1308260.
48. Alnaim LS, Almalki HM, Almutairi AM, et al. The prevalence of drug-drug interactions in cancer therapy and the clinical outcomes. Life Sci. 2022;310:121071.
49. Wang H, Shi H, Wang N, et al. Prevalence of potential drug - drug interactions in the cardiothoracic intensive care unit patients in a Chinese tertiary care teaching hospital. BMC Pharmacol Toxicol 2022;23:39.

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