Original Research Article

Journal of College of Medical Sciences-Nepal, Vol-22, No.2, Apr-Jun 2026

ISSN: 2091-0657 (Print); 2091-0673 (Online) Open Access
DOI: 10.3126/jcms.v22i2.89234

Potential Drug-Drug Interactions in Patients Admitted to Intensive Care Unit of a Tertiary Care Hospital in Nepal: A Descriptive Cross-Sectional Study

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ABSTRACT

Background

Potential drug-drug interactions (pDDIs) are a major concern in Intensive Care Units (ICUs) due to polypharmacy, severe illness, and complex treatment regimens. These interactions can lead to adverse clinical outcomes. This study aimed to determine the prevalence, severity, and predictors of pDDIs among ICU patients in a tertiary care teaching hospital in Nepal.

Methods

A descriptive cross-sectional study was conducted among 150 ICU patients at Universal College of Medical Sciences from Nov 2023 to April 2024. Patient demographics and drug profiles were collected from Cardex records. The pDDIs were identified using the Medscape drug interaction checker and classified by severity. Binary logistic regression was performed to identify predictors, and results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

Among 150 patients, 118 (78.67%) had at least one pDDIs. A total of 433 interactions were identified from 1074 prescribed medications, with an average of 7.16 drugs per patient. Most interactions were classified as 'monitor closely' (53.35%), followed by minor (31.4%), serious (13.6%), and contraindicated (1.6%). Polypharmacy was observed in 71.3% of patients. It was the only significant predictor of pDDI (AOR=9.33, 95% CI: 3.78-23.2, $p<0.001$).

Conclusions

The pDDIs are highly prevalent among ICU patients. Polypharmacy is the main independent predictor, while age and comorbidities are not significantly associated. The finding highlights the importance of careful medication review and further studies to assess their clinical relevance.

Keywords: Drug-Drug Interactions; Intensive Care Unit; Patient safety; Prevalence.

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INTRODUCTION

Medicines play a crucial role in disease prevention, recovery, and improving the quality of life, but may also cause adverse outcomes due to drug interactions.[1] In intensive care units (ICUs), critically ill patients require complex pharmacotherapy, increasing the risk of potential drug-drug interactions (pDDIs).[2, 3] These interactions, which may be pharmacokinetic or pharmacodynamic, can alter drug effectiveness or toxicity, and their incidence rises with polypharmacy.[4, 5] Elderly patients with comorbidities are particularly at risk, often leading to serious consequences and increased healthcare costs.[6] ICU patients are particularly vulnerable to pDDIs due to disease severity, polypharmacy, comorbidities, complex regimens, and frequent medication changes.[7] Despite this risk, evidence from Nepal, particularly in tertiary care teaching hospitals, on the prevalence and patterns of pDDIs remains limited. Therefore, this study aimed to evaluate local evidence to support safer prescribing and improved monitoring in ICU settings.

METHODS

Study Area

The study was conducted in the Medical Intensive Care Unit (MICU), Coronary Care Unit (CCU), and Surgical Intensive Care Unit (SICU) at Universal College of Medical Sciences and Teaching Hospital.

Study Design

A hospital-based descriptive cross-sectional study was conducted over the period of six months.

Sample size and sampling

A consecutive sampling technique was used to enroll all eligible patients during the study period. A total of 150 patients were included in the study. Patients aged 18 years and above who were admitted for more than 24 hours and prescribed two or more medications were included. Patients receiving only topical medications, nutritional supplements, or a single medication were excluded. Patients with incomplete medical records and those whose caregivers declined consent were also excluded from the study.

Data Collection

The study was conducted over the period of six months (November 2023 to April 2024). Ethical approval was obtained from the Institutional Review Committee, Universal College of Medical Sciences (Ref. No.: UCMS/IRC/067/23). Data were collected using a structured case proforma from Cardex records. Information regarding demographic details, diagnosis, comorbidities, and prescribed medications was recorded. Records with missing or incomplete key variables were excluded to maintain data quality. Potential drug-drug interactions (pDDIs) were defined as interactions identified through a standardized database without confirmation of clinical manifestation. The Medscape drug interaction checker was used due to its accessibility and comprehensive classification of interaction severity.

Table 1: Illustrates the pDDIs categorized by Medscape database.

Severity	Description
Serious (Use alternative)	Requires alternative drugs due to significant clinical risks.
Contraindicated	Drugs should not be co-administered due to high risks.
Monitor closely	Requires close patient monitoring for adverse effects.
Minor	Minimal clinical impact, no treatment changes needed.

Data Analysis

Data were entered into Microsoft Excel and analysed using SPSS version 20 (Statistical Package for the Social Sciences). Descriptive statistics were presented as frequency and percentage. The prevalence of pDDIs was calculated and presented with 95% confidence intervals (CI). Binary logistic regression analysis was performed to estimate unadjusted and adjusted odds ratio for presence of pDDIs. The independent variables included age group, the presence of comorbidities, and number of medications prescribed. A p-value of < 0.05 was considered statistically significant.

RESULTS

Among 150 patients, the majority, 49 (32.7%), were in the 51-70 age range, followed by the 31-50 age range, 41 (27.3%). The gender distribution was nearly equal, with males representing 76 (50.7%) and females comprising 74 (49.3%). The total number of medications prescribed in this study is presented in Table 2. The majority of patients, 107 (71.3%), received more than five medications, while 43 (28.7%) were administered fewer than five medications.

Table 2: Distribution of patients according to age group, gender, and number of medications (n=150).

Characteristics	Frequency n (%)
Age Group (years)	
18-30	28 (18.7)
31-50	41 (27.3)
51-70	49 (32.7)
>70	32 (21.3)
Sex	
Male	76 (50.7)
Female	74 (49.3)
Number of medications	
≤5	43 (28.7)
>5	107 (71.3)

The most commonly identified pDDIs, along with their possible consequences, are presented in (Table 4).

Out of 150 patients, 118 (78.7%) experienced at least one potential drug-drug interaction (pDDIs), while 32 (21.3%) had no interactions. A total of 1074 medications were prescribed, with an average of 7.16 drugs per patient. The severity of pDDIs based on classification using the Medscape drug interaction checker: most identified interactions belong to the 'monitor closely' 231 (53.3%) category, followed by minor 136 (31.4%), while serious interactions 59 (13.6%) and contraindicated 7 (1.6%) were less frequent (Table 3).

Table 3: Distribution of patients according to presence and severity of potential drug-drug interactions (pDDIs) (n=150).

Characteristics	Frequency n (%)
Presence of pDDI (n=150)	
Patients with interactions	118 (78.67)
Patients without interactions	32 (21.33)
Severity of pDDI (n=433)	
Serious	59 (13.63)
Contraindicated	7 (1.62)
Monitor closely	231 (53.35)
Minor	136 (31.40)

Note: The overall prevalence of pDDIs was 78.7% (95% CI: 71.9–84.3). Total pDDIs = 433 interactions among 118 patients

Table 4: Most frequently identified pDDIs and their potential consequences (n=433).

Interacting pairs	Frequency n (%)	Severity	Potential consequences
Metronidazole +Fentanyl	7 (11.9)	Serious	Increased fentanyl effect --sedation/ respiratory depression
Fentanyl+Tramadol	5 (8.5)	Serious	Additive CNS depression
Levetriacetam+Tramadol	5 (8.5)	Serious	Increased sedation
Haloperidol+Ondansetron	4 (6.8)	Serious	QT prolongation
Piperacillin +Enoxaparin	3 (5.1)	Serious	Increased bleeding risk
Ceftriaxone+Calcium gluconate	2 (28.5)	Contraindicated	precipitation risk
Amikacin +Amphotericin B deoxycholate	1 (14.3)	Contraindicated	Nephrotoxicity/ototoxicity
Doxycycline+Tretinoin	1 (14.3)	Contraindicated	Increase intracranial pressure
Linezolid +Norepinephrine	1 (14.3)	Contraindicated	Hypertensive crisis
Levetriacetam +Acetaminophen	23 (16.9)	Minor	Reduced analgesic effects
Metronidazole+Acetaminophen	11 (8.1)	Minor	Altered metabolism
Hydrocortisone+Insulin	8 (5.9)	Minor	Reduced insulin effect
Hydrocortisone+Amlodipine	8 (5.9)	Minor	Reduced antihypertensive effect
Ceftriaxone+Furosemide	6 (4.4)	Minor	Increased nephrotoxicity risk

Labetalol+ Amlodipine	14 (6.1)	Monitor closely	Hypotension risk
Prazosin+Amlodipine	13 (5.6)	Monitor closely	Hypotension risk
Levetriacetam+Haloperidol	8 (3.5)	Monitor closely	Increased sedation
Metronidazole+Hydrocortisone	9 (3.9)	Monitor closely	Increased steroid effect
Levofloxacin+Hydrocortisone	9 (3.9)	Monitor closely	Tendon rupture risk

The most prevalent combination in the severe category was metronidazole + fentanyl. The combination of Labetalol + Amlodipine is classified as requiring close monitoring, while Levetriacetam + Acetaminophen are categorized as minor interactions. The logistic regression model, which shows the number of medications (>5), was the only significant predictor of potential drug-drug interactions (pDDIs), showing higher odds in both unadjusted (OR=10.16, p<0.001) and adjusted (AOR=9.33, 95% CI: 3.78-23.02, p<0.001). Comorbidities were not significantly associated with pDDIs after adjustment (AOR=2.17, 95% CI: 0.68-6.93, p=0.193). Similarly, age group showed no statistically significant association with pDDIs in the adjusted model (Table 5).

Table 5: Predictors of potential drug-drug interactions (pDDIs)

Characteristics	Unadjusted OR	P-value	Adjusted OR	P-value	95%CI of adjusted OR
No. of medications	10.16	<0.001	9.33	<0.001	3.78-23.02
Comorbidities	2.57	0.073	2.17	0.193	0.68-6.93
Age Group (years)					
31-50	2.41	0.144	1.66	0.469	0.42-6.51
51-70	0.602	0.44	0.531	0.399	0.13-2.24
>70	1.25	0.69	1.1	0.883	0.31-3.90

Binary logistic regression test used. OR=odds ratio; CI=confidence interval

***Note**: Reference category for age is (18-30 years). Gender was not adjusted for confounders as its unadjusted P-value was 0.932(OR=0.967)*

DISCUSSION

The present research presents significant findings regarding the prevalence and severity of potential drug-drug interactions (pDDIs) among hospitalized patients in the intensive care unit of a tertiary care hospital in Nepal. The prevalence of potential drug-drug interactions (pDDIs) was 78.7% among 150 ICU patients. A total of 433 interactions were observed among 1074 prescribed medications, leading to an average of 7.16 medications per patient. This demonstrates that the ICU setting is more vulnerable to pDDIs because of factors like severe illness and polypharmacy. These interactions may result in adverse outcomes, longer hospital stays, higher medical expenses, and higher mortality rates.

The prevalence of potential drug-drug interactions (pDDIs) observed in this study is consistent with the findings of *Bhandari et al*.,[8] at Tribhuvan University Teaching Hospital (TUTH), which indicated a pDDI prevalence of 78.3% among 382 discharge prescriptions. Similarly, a study at a tertiary care hospital in Pune, India, found a prevalence of pDDIs of 76.5% among the 183 participants.[1] In contrast, *Ghimire et al.,*[6] observed that the prevalence of pDDIs was higher in their research on TUTH ICU patients, reporting a prevalence of 89.11% among 101 patients. Furthermore, 83.25% of elderly patients hospitalized in the intensive care unit at another tertiary care facility had pDDIs, according to *Shetty et al*.,[3] However, research by *Pal et al*.,[9] and *Salwe KJ et al.,*[10] which reported prevalence of 67.28% and 52.69%, respectively, showed a lower prevalence of pDDIs.

A number of factors, such as variation in study sites, populations, prescribing patterns, the critical condition of patients in intensive care unit, polypharmacy, comorbidities, and the pDDIs

checking software used, may be responsible for the variation in the prevalence of potential drug-drug interactions (pDDIs) across different studies.

Numerous studies have indicated a male predominance in socio-demographic characteristics, aligning with the finding of the current study.[1, 11, 12] On the other hand, a study by *Jimmy OD et al.,* found that women had a greater incidence of pDDIs (56.52%).[13] These disparities might result from the fact that their study included a greater proportion of female patients.

The current study included patients aged 18 to 90 years, with the majority experiencing potential drug-drug interactions (pDDIs) in the 51-70 age group (32.7%). This finding aligns with results from several other studies.[1, 8, 11, 14] Elderly individuals, particularly those in critically ill conditions, are more likely to experience pDDIs because they are exposed to more drugs. Furthermore, older persons with comorbidities frequently need to take multiple medications for an extended period of time, which increases the risk of drug interactions. Elderly patients are therefore especially susceptible to pDDIs.

Numerous studies indicate comparable average drug counts per patient, demonstrating a significant correlation between polypharmacy and increased rates of drug interactions. The current study reports an average of 7.16 drugs used per patient, consistent with findings from *Acharya et al.,*[7] On the other hand, *Upreti et al*.,[5] and *Gupta et al.,*[1] reported an average of 8.56 and 8.25 medications per prescription, respectively. These discrepancies may be ascribed to variation among study populations, the patients' medical conditions, treatment necessities, and disparities in the prescribed medications.

According to Medscape software, the most prevalent potential drug-drug interactions (pDDIs) in the current study were categorized as 'monitor closely' (53.35%). This result aligns with the study conducted by *Hamid et al.,*[4] which reported 52%, and *Giri et al.,*[15] which reported 57.79%. However, the study by *Jain et al.,*[16] found a larger percentage in the 'monitor closely' category (71.29%), whereas the study by *Pal et al*.,[9] found a lower percentage of 28.5%.

The current study identified a 31.4% incidence in the minor interaction category, aligning with the results reported by *Giri et al.,*[15] In comparison to the current study, *Hamid et al*.,[4] reported a greater prevalence of 43%, whereas *Pal et al*.,[9] reported a lower incidence of 10.6%. Differences in the studies' sample sizes could be the cause of these discrepancies.

The pattern observed, where moderate severity interactions account for a significant number of cases, which was noted in studies by *Ghimire et al.,*[6] 63.46% and *Bhandari et al*.,[8] 76.5%. This disparity may result from variations in the classification systems employed in the interaction database (e.g., Medscape, Lexicom) and the particular drug combinations found in the study populations.

The significant proportion of interactions classified as 'monitor closely' suggests that cautious monitoring of potential drug interactions is consistently necessary across various populations and healthcare settings. Addressing these concerns can be achieved through interventions like continuing medical education programs designed for healthcare practioners. Additionally, the presence of 1.62% of interactions classified as contraindicated, though small, is particularly alarming as it highlights the necessity of absolute drug combinations that should be avoided. The current investigation found a number of interactions that are clinically significant. Metronidazole and fentanyl were the most frequent potential drug-drug interactions (pDDIs) among the severe group, which can raise the risk of sedation and respiratory depression. Furthermore, the combination of ceftriaxone and calcium gluconate is not recommended because of the known hazard of particulate precipitation. The predominant interaction observed was between levetriacetam and acetaminophen, classified as minor. Levetriacetam diminishes the effectiveness of acetaminophen, a drug interaction frequently neglected by healthcare professionals in their hectic clinical situations.

Furthermore, the combination of labetalol or prazosin with amlodipine falls into the 'monitor

closely' category. This illustrates the necessity of constant monitoring to avoid hypotension and reflects the widespread need for a combination of antihypertensive medication in critically ill patients. Several research studies, such as those conducted by *Ghimire et al.,*[6] *Upreti et al.*,[5] *Acharya et al.,*[7] *Dinesh et al.,*[17] have reported a variety of drug interactions. The discrepancies might be due to comorbidities, different diagnoses, clinical situations in the intensive care unit, and changes in medication prescription patterns.

In this study, polypharmacy (>5 medications) was the only significant predictor of potential drug-drug interactions (pDDIs), showing a strong independent association after adjustment. Patients receiving more than five medications had nearly nine times odds of pDDIs, which confirms polypharmacy as the key risk factor. This finding is consistent with various studies.[8, 18, 19] In contrast, comorbidities were not independently associated with pDDIs after adjustment in the present study. Although initially associated with unadjusted analysis, the effect was through increased medication use. This is consistent with the study conducted by *Y. Arslan et al.,*[19] Similarly, age was not significantly associated with pDDIs after adjustment. Although older age is traditionally considered a risk factor, our findings suggest that its effect is largely explained by medication burden.

Thus, the finding shows that polypharmacy is the primary modifiable determinant of pDDIs, while age and comorbidities influence risk indirectly through increased medication exposure. This underscores the importance of rational prescribing and regular medication review to reduce preventable drug interactions.

Limitations

This study has several limitations. As the study was conducted in a single tertiary care ICU, which may limit the generalis ability of the findings to other settings. The study assessed only potential drug-drug interactions (pDDIs) rather than clinically manifested outcomes, so the actual clinical impact of these interactions could not be evaluated. The identification of pDDIs was based on single-interaction-checking software (Medscape), which may differ from other databases and could lead to variation in classification. The cross-sectional design does not allow assessment of causality or temporal relationships between risk factors and pDDIs.

Conclusions

The present study showed a high prevalence of potential drug-drug interactions among ICU patients, highlighting a significant patient safety concern in critical care settings. Polypharmacy was identified as the strongest independent predictor of pDDIs, while age and comorbidities were not significant after adjustment. These findings emphasise the importance of rational prescribing and regular medication review to minimise preventable drug interactions and improve patient safety in ICU settings.

Ethics approval: Ethical approval was obtained from the Institutional Review Committee, Universal College of Medical Sciences (Ref. No.: UCMS/IRC/067/23).

Conflict of interest: The author declares no conflict of interest

Funding: No funding was received for this study

Availability of data and materials: All data analysed during this study will be made available upon reasonable request from the corresponding author.

Author contributions

Conceptualization: Laxmi Shrestha
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Investigation: Bigin Gyawali
Methodology: Laxmi Shrestha
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Citation: Shrestha L, Gyawali B, Palikhey A, Joshi B, Shrivastava AK. Potential Drug-Drug Interactions in Patients Admitted to Intensive Care Unit of a Tertiary Care Hospital in Nepal: A Descriptive Cross-Sectional Study. J Coll Med Sci-Nepal. 2026 Jun. 30;22(2). 149-56.