

The Relationship Between Polypharmacy and Potential Drug Interactions in ICU Patients at Al-Ihsan Regional General Hospital 2024

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Abstract. Intensive Care Unit (ICU) patients with critical conditions and comorbidities require complex pharmacological interventions that lead to polypharmacy, thereby increasing the risk of potential drug-drug interactions (pDDIs). This study aimed to analyze the correlation between polypharmacy and pDDIs among adult patients in the ICU of Al-Ihsan Regional General Hospital, Bandung. This study utilizes the method of an analytical observational design with a cross-sectional approach, involving 99 medical records from the 2024 period selected through a total sampling technique. Potential drug interactions were identified using the Lexicomp database, and data were analyzed using the Spearman Rank correlation test. The results showed that the majority (46.5%) of patients experienced major polypharmacy (>5 drugs). The prevalence of pDDIs increased with the number of drugs administered, dominated by moderate and major interactions. The highest prevalence was observed in the major polypharmacy group (65%), significantly exceeding the moderate (44%) and minor (17%) groups. Statistical analysis demonstrated a significant positive correlation with moderate strength between polypharmacy and pDDIs ($r = 0.416$; $p = 0.000$). A crucial finding indicated that even patients receiving 2-3 drugs (minor polypharmacy) remained at risk for major severity pDDIs. It is concluded that an increased degree of polypharmacy correlates significantly with an elevated risk of pDDIs. This underscores the necessity for clinical vigilance across all levels of polypharmacy in the ICU.

Keywords: *Drug Interactions, Polypharmacy, RSUD Al-Ihsan.*

A. Introduction

Patient safety is a global priority in healthcare services, considering that approximately 10% of patients experience adverse events annually, including those resulting from medication side effects.[1] A primary driver of this issue is polypharmacy, defined as the concurrent use of two to more than eleven types of medications, categorized into minor (2–3 drugs), moderate (4–5 drugs), and major (>5 drugs) levels. This practice is highly prevalent, with rates reaching 52% among hospitalized patients and 45% in the elderly.[2], [3] In Indonesia, the situation is even more concerning, as evidenced by a study recording polypharmacy rates as high as 87.5% in hospitalized geriatric patients.[4]

An elevated medication burden is positively correlated with the risk of potential drug interactions (pDDIs), a condition characterized by alterations in a drug's pharmacological activity or safety profile. Such modifications occur when the effect of a primary drug is influenced by the presence of other medications, dietary factors, herbal preparations, or chemical agents.[2], [5], [6], [7] Drug-drug interactions (DDIs) represent a major contributor to patient safety concerns, accounting for approximately 5% of all adverse drug reactions (ADRs) in hospital settings, the majority of which are preventable. Globally, DDIs are identified as the underlying cause in roughly 21% of hospitalizations related to adverse drug events (ADEs).[1], [6] This risk becomes critical for patients in the Intensive Care Unit (ICU) due to the complexity of therapies required to manage their critical conditions.[8], [9] Studies indicate that the risk of pDDIs in the ICU reaches 54%, a figure twice as high as that of other nursing units.[8] Furthermore, a study in Brazil found that nearly 90% of ICU patient prescriptions contained at least one potential drug interaction.[10]

The clinical implications of polypharmacy and drug-drug interactions significantly undermine patient safety by escalating morbidity and mortality rates, which exhibit a linear correlation with the number of medications consumed. Scientific literature suggests that each additional medication increases the risk of mortality by approximately 3%, while the prevalence of geriatric syndromes, such as frailty, reaches 75% among polypharmacy users. Beyond inducing interactions and adverse drug reactions that compromise clinical outcomes, a high medication burden is associated with a 21% increase in the incidence of falls, as well as cognitive decline and a heightened risk of dementia, particularly with psychotropic drug use. Collectively, this spectrum of clinical consequences accelerates physical deterioration and increases vulnerability to functional disability and frequent hospitalization, ultimately diminishing the overall quality of life.[11], [12]

The clinical spectrum of drug-drug interactions (DDIs) is exceptionally broad, ranging from subtle, difficult-to-detect manifestations to fatal outcomes resulting from therapeutic failure or increased toxicity. Classified by severity as minor, moderate, or major, these interactions collectively drive increases in morbidity, mortality, and healthcare expenditures. Within the ICU environment, this complexity is particularly evident across various therapeutic classes; for instance, interactions involving central nervous system agents such as morphine, metoclopramide, and tramadol can potentiate depressive effects and lead to complications like urinary retention. Similarly, cardiovascular and metabolic combinations involving furosemide, methylprednisolone, and insulin pose risks of electrolyte imbalances and diminished efficacy in diuretic and antidiabetic regimens. These clinical risks are further underscored by findings from Soba University Hospital, which highlighted elevated bleeding risks from aspirin-enoxaparin combinations and major hyperkalemia from spironolactone-KCl interactions. Furthermore, respiratory synergies like budesonide and clarithromycin warrant close monitoring as they may compromise essential prokinetic effects in critically ill patients.[1], [2], [7], [9], [13] The identification of these interactions can be facilitated through various electronic reference databases, such as Drugs.com, Lexicomp, Medscape, Micromedex, and Epocrates. Notably, Lexicomp has been documented to demonstrate the highest diagnostic performance, yielding a sensitivity of 92% and an accuracy of 86%.[13]

The risk of potential drug-drug interactions (pDDIs) is driven by a complex convergence of multidimensional risk factors, spanning from socio-demographic variables to intricate clinical circumstances. Epidemiologically, polypharmacy is significantly influenced by advanced age, social isolation (such as living alone), migration backgrounds, and the cumulative burden of multimorbidity, all of which necessitate long-term pharmacological interventions. Within the Intensive Care Unit (ICU) setting, the probability of pDDIs reaches its zenith due to the implementation of highly complex therapeutic regimens, the administration of a massive quantity of

medications for patient stabilization, and extended lengths of stay. This vulnerability is further exacerbated by the systemic physiological dysfunction accompanying critical illness and the biological aging process, both of which augment target organ sensitivity to therapeutic agents. For instance, age-related alterations in the central nervous system result in heightened pharmacodynamic responsiveness to the depressant effects of opioids and benzodiazepines, clinically manifesting as an elevated risk of respiratory depression and cognitive impairment a condition further compromised by substantial declines in hepatic metabolism and renal filtration, which impair drug clearance from the systemic circulation. Consequently, the subsequent accumulation of drug concentrations in the bloodstream exponentially escalates the risk of toxicity and severe adverse events resulting from DDIs, ultimately compromising patient safety and deteriorating clinical outcomes in critically ill populations.[5], [9], [13]

Given these substantial risks, this study was conducted at RSUD Al-Ihsan Bandung to analyze the relationship between polypharmacy and potential drug-drug interactions in adult ICU patients. Furthermore, this study aims to provide a clear descriptive overview of the distribution of polypharmacy categories and the severity levels of the interactions. The findings of this study are expected to enhance clinical vigilance in medication therapy management within intensive care units.

B. Method

This study employed an observational analytic design with a cross-sectional approach. The target population comprised all adult patients admitted to the Intensive Care Unit (ICU) at RSUD Al-Ihsan Bandung, while the accessible population included patients treated between January and December 2024.

The sampling was conducted using a total sampling technique. Inclusion criteria were patients aged ≥ 18 years, possessing complete medical records, and receiving ≥ 2 types of medications. Exclusion criteria included patients who passed away before their medication therapy was fully documented and those receiving only supportive therapy without pharmacological intervention. Based on the Slovin formula, the minimum required sample size was 94; however, this study successfully recruited 99 medical records that fulfilled the inclusion criteria and met none of the exclusion criteria.

The independent variable in this study was the level of polypharmacy (minor, moderate, and major). The dependent variable was the level of potential drug-drug interactions (pDDIs), assessed using the Lexicomp database (categorized as none, minor, moderate, and major). Data analysis included univariate analysis for frequency distribution and bivariate analysis using the Spearman's Rank Correlation test. This research received ethical clearance from the Health Research Ethics Committee (Number: 094/KEPK-Unisba/IX/2025).

C. Result and Discussion

This study was conducted on adult patients in the Intensive Care Unit (ICU) of RSUD Al-Ihsan Bandung during the 2024 period. A total of 99 medical records were analyzed, providing comprehensive data on medication use profiles within this population. The frequency distribution of polypharmacy occurrences is presented in the following table.

Table 1. Frequency Distribution of Polypharmacy Prevalence among Adult Patients in The Intensive Care Unit of RSUD Al-Ihsan during 2024

Polypharmacy Categories	Number of Patients	Frequency
Minor	18	18,2%
Moderat	35	35,3%
Mayor	46	46,5%
Total	99	100%

Frequency distribution analysis in table 1 reveals that the medication profiles of ICU patients are predominantly characterized by major polypharmacy, with a prevalence of 46.5%. This finding indicates that nearly half of the study population received more than five medications daily, a condition that underscores the critical illness status and complex medical needs of ICU patients requiring aggressive pharmacological interventions. Such high rates of polypharmacy are consistent with existing literature, which suggests that intensive care patients necessitate extensive therapeutic regimens to stabilize organ failure. Beyond the severity of the critical condition, advanced age was also identified as a significant factor driving high medication burdens, further emphasizing the relevance of these findings for optimizing therapeutic management within the intensive care setting.[14] Building upon these observations, a secondary analysis was undertaken to determine the distribution of potential drug interaction severity relative to polypharmacy status. The specifics of interaction level distribution across various polypharmacy categories are illustrated in the table below.

Table 2. Distribution of Potential Drug-Drug Interaction Severity Levels by polypharmacy Category

Potential Drug Interaction Severity	Minor		Polypharmacy Level Moderate		Major	
	Number	N (%)	Number	N (%)	Number	N (%)
No Interaction	24	82,76%	45	55,56%	43	34,96%
Minor	0	0%	2	2,47%	9	7,32%
Moderate	4	13,79%	28	34,57%	51	41,46%
Major	1	3,45%	6	7,41%	20	16,26%
Total	29	100%	81	100%	123	100%

Data analysis in table 2 reveals a significant shift in risk patterns, where the proportion of patients without potential drug-drug interactions (pDDIs) sharply declines from over 80% in the minor polypharmacy category to below 40% as the degree of polypharmacy escalates. These findings confirm a linear correlation between the number of medications prescribed and the risk of interactions, with moderate-severity pDDIs emerging as the predominant finding across all levels of polypharmacy. A particularly critical observation is the nearly fivefold increase in the prevalence of major interactions within the major polypharmacy group compared to the minor group; nevertheless, the presence of major pDDIs in 3.45% of patients with minor polypharmacy remains a significant clinical concern. Ultimately, these data underscore that an increasing medication burden not only broadens the interaction spectrum but also exponentially elevates the risk of severe clinical complications within the intensive care setting. Furthermore, to validate these findings, an analysis of the relationship between polypharmacy and pDDIs was performed using the Spearman's Rank Correlation test to determine the direction and strength of the association.

Table 3. Association between Polypharmacy and Potential Drug-Drug Interactions

Potential Drug Interaction Severity	Polypharmacy			p-Value*	r-Value
	Minor N (%)	Moderate N (%)	Major N (%)		
No Interaction	82,76%	55,56%	34,96%	0,000	0,416
Minor	0%	2,47%	7,32%		
Moderate	13,79%	34,57%	41,46%		
Major	3,45%	7,41%	16,26%		

Note: *the p-value is calculated using Spearman's rank test

The Rank Spearman correlation analysis presented in Table 3 confirms a statistically significant positive relationship between polypharmacy and potential drug-drug interactions, with a significance value of $p=0.000$ ($p<0.01$) and a correlation coefficient of $r=0.416$. Given that the coefficient falls within the 0.40–0.59 range, the strength of this association is classified as moderate. These findings clinically demonstrate a linear progression where an increase in the number of

medications administered representing a higher degree of polypharmacy directly correlates with a greater likelihood of potential drug interactions, thereby underscoring the necessity for enhanced pharmacological monitoring as treatment complexity increases.

This is consistent with a 2021 study by Demirkapu, which stated that ICU patients face a twofold higher risk of drug-drug interactions (DDIs) compared to general ward patients due to the high medication burden.[9] The significant correlation identified between polypharmacy and potential drug-drug interactions (pDDIs) in this study is consistent with research conducted by Febriyani in 2024 among chronic kidney disease patients. That study established that polypharmacy significantly contributes to the escalation of interaction risks, reinforcing the principle that a high medication burden is a primary determinant of pharmacotherapeutic safety.[15]

The mechanisms of drug interactions are broadly classified into pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic (PK) interactions occur when co-administered agents alter the systemic concentration of a drug by interfering with its absorption, distribution, metabolism, or excretion (ADME) processes, thereby modulating its therapeutic efficacy or toxicity profile. During the absorption phase, ketoconazole can enhance the uptake of medications such as midazolam through P-glycoprotein (P-gp) inhibition, while antacids may impede the absorption of acid-dependent drugs by elevating gastric pH. In the distribution phase, competition for plasma protein binding sites notably observed with warfarin can lead to increased free drug fractions and heightened toxicity risks. Metabolism serves as the most frequent site for interactions, primarily mediated by hepatic enzymes such as CYP3A4; for instance, ritonavir inhibits CYP3A4 to potentiate lopinavir levels, whereas rifampicin acts as an enzyme inducer, potentially reducing therapeutic effectiveness. Finally, in the excretion phase, interactions within the kidneys such as probenecid inhibiting renal secretion can significantly elevate the systemic concentrations of drugs like penicillin.[2], [9], [16].

Pharmacodynamic interactions occur at the receptor or target system level without altering systemic drug concentrations, but rather by modifying physiological responses through synergistic or antagonistic mechanisms. In the Intensive Care Unit (ICU) setting, these interactions represent a frequent and critical clinical challenge, as they can trigger severe adverse events or significantly diminish therapeutic efficacy. This is particularly evident in the synergistic combination of central nervous system agents such as morphine, tramadol, and benzodiazepines which markedly elevates the risk of respiratory depression. Conversely, antagonistic interactions, such as those between ACE inhibitors and NSAIDs, can compromise blood pressure control. Furthermore, interactions involving cardiovascular medications, notably the co-administration of furosemide and methylprednisolone, warrant rigorous monitoring due to the risk of electrolyte imbalances and the overall inhibition of therapeutic effectiveness. Understanding these mechanisms is essential for safeguarding patient safety and optimizing clinical outcomes in intensive care.[2], [9], [16]

Conversely, the results of this study contradict the findings of Baiq in 2025 regarding Congestive Heart Failure (CHF) patients and Nursela in 2025 concerning type 2 Diabetes Mellitus patients, neither of whom identified a significant relationship between polypharmacy and pDDIs.[17], [18] These discrepancies may be attributed to three primary factors, the first and second factors are methodological in nature, involving variations in polypharmacy definitions that influence the study's statistical power, as well as discrepancies between reference databases (such as Lexicomp and Micromedex) which utilize distinct sensitivity levels and severity classification algorithms. The third factor pertains to the clinical characteristics of the population, as the physiological complexity of critically ill patients in the ICU presents a significantly different profile compared to geriatric patients.[19] Studies by Fatemeh in 2021 and Marwan in 2021 concluded that the specialty of the prescribing physician and specific disease types, particularly cardiovascular conditions, contribute significantly to an increased risk of interactions.[20], [21].

The findings of this research necessitate a shift in therapeutic management. The high prevalence of moderate and major pDDIs underscores the need for the implementation of a Clinical Decision Support System (CDSS) integrated with electronic medical records. A 2024 study by Li demonstrated that CDSS can reduce prescribing error risks by up to 50%. However, significant challenges persist regarding its widespread adoption, primarily due to integration issues with Hospital Information Systems (HIS), which impede practitioners' ability to access relevant information efficiently. Furthermore, post-implementation risks such as alert fatigue where a high

volume of low-priority interaction warnings may lead clinicians to overlook critical notifications remain a crucial concern that must be addressed to ensure patient safety.[22], [23]

Effective risk mitigation for drug-drug interactions (DDIs) in the intensive care setting necessitates an integrated framework that leverages safety technologies, specialized expertise, and robust interprofessional synergy. Central to this strategy is the active integration of clinical pharmacologists into daily clinical rounds. Their specialized proficiency in evaluating intricate medication regimens, conducting pharmacovigilance, and formulating precision therapeutic interventions grounded in pharmacokinetics and pharmacodynamics (PK/PD) makes them an indispensable asset for patient safety.[24], [25] This leadership role must be supported by the optimization of daily bedside tools, such as the FAST HUG framework (Feeding, Analgesia, Sedation, Thromboembolic prophylaxis, Head of bed elevation, stress Ulcer prophylaxis, and Glycaemic control), as a systematic evaluation standard to ensure medication appropriateness and minimize unnecessary polypharmacy. Ultimately, the integration of expert oversight with structured clinical monitoring will guarantee more accurate risk-benefit evaluations, effective management of interaction alerts, and the continuous enhancement of treatment quality and patient safety.[10], [26].

D. Conclusion

This study concludes that the medication profiles of adult patients in the Intensive Care Unit (ICU) of RSUD Al-Ihsan Bandung are predominated by major polypharmacy (46.5%). There is a statistically significant and directly proportional relationship between the level of polypharmacy and potential drug-drug interactions (pDDIs), characterized by an escalating risk of interactions as the number of administered medications increases. A distinct shift was observed from a majority of patients without interactions in the minor polypharmacy category toward moderate pDDIs as the medication burden intensified. Furthermore, the identification of major-severity interactions even within the minor polypharmacy group underscores the urgent necessity for stringent clinical vigilance and rigorous medication therapy management, particularly within the intensive care setting.

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