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Prevalence and Associated Factors of Drug-Drug Interactions in Hospitalized Diabetic Patients: A Cross-Sectional Study

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ABSTRACT: Diabetes mellitus is a chronic metabolic condition frequently associated with complications and comorbidities that often require hospitalization for effective management. Such patients are often prescribed with multiple medications, which elevate the risk of potential drug-drug interactions (pDDIs). Hence, this study aims to determine the prevalence, severity, common interacting pairs, and factors associated with pDDIs among hospitalized diabetes patients**.** The study used a retrospective cross-sectional study design conducted at Universitas Indonesia Hospital. Lexicomp® Lexi-Interact™ software was used to analyze and classify pDDIs. Logistic regression analysis was used to identify different factors associated with the presence of pDDIs. Among 200 patients included in the study, about half (50.5%) of the patients were male. The median age was 60 years, with an interquartile range of 52-69 years. PDDIs were observed in 89% of patients. A total of 966 interactions were found, of which 75.6% were moderate, 16.2% were minor, and 8.1% were of major severity. Meanwhile, in the risk rating C category, 71.0% were predominant, followed by B and D, 15.0% and 11.0%, respectively. Multivariate regression analysis showed a statistically significant association of pDDIs with 5–8 prescribed medicines (OR=22.8; 95% CI=5.5-94.7; p<0.001), >8 prescribed medicines (OR=64.4; 95% CI=11.3-336.5; p<0.001). PDDIs are highly prevalent in diabetic patients. Moderate types of interaction with a risk rating of C and a reliability rating of fair are commonly found. The most common drug-interacting pairs are metformin + ondansetron and atorvastatin + amlodipine. Polypharmacy is observed as a risk factor for PDDIs occurrence.

Keywords: **prevalence; diabetes mellitus; drug-drug interaction; risk factor, Indonesia.**

Introduction

Diabetes mellitus is a chronic disease that imposes considerable problems on the global healthcare system due to its high prevalence, complexity in management, and associated economic burden [1]. According to the International Diabetes Federation, 537 million adults are living with diabetes globally, with a projection of a significant increase to 783 million by 2045 [2,3]. Indonesia, which holds the seventh rank worldwide in diabetes prevalence, is anticipated to increase the number of cases from 10.2 million in 2017 to 16.7 million by 2045 [4,5]. Additionally, it is important to note that, according to Oktora & Butar, Jakarta had the highest prevalence in Indonesia at 3.4% in 2022 [3].

Patients with diabetes frequently face a wide range of comorbidities, including hypertension, dyslipidemia, retinopathy, nephropathy, and neuropathy [6]. These associated conditions not only worsen the primary disease but also increase the risk of developing cardiovascular diseases, kidney failure, and other systemic complications [7]. Furthermore, those with diabetes are susceptible to poor wound healing, which increases the risk of infection [8]**.** The proper management of diabetes and its associated comorbidities is crucial for retarding the progression of disease and reducing mortality [9]**.** This tends to complicate the pharmacological treatment and necessitate the use of multiple medications in the management of patients with diabetes, leading to the frequent practice of polypharmacy [10]**.** The consequences of polypharmacy include poor compliance with medications, increased healthcare expenses, and, most notably, drug-drug interaction (DDIs) [11].

DDIs can be defined as the pharmacological effects of one drug being influenced and

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modified by the concomitant administration of another drug, directly or indirectly [12]. This can lead to treatment failure from antagonistic effects or induce drug toxicity through synergistic or additive mechanisms [12]. DDIs can arise from various processes, such as the drugs' pharmacokinetics (PK) or pharmacodynamic (PD) characteristics, leading to changes in treatment efficacy and causing adverse drug reactions (ADRs) [13].

DDIs are a primary clinical concern, accounting for 3% of all hospital admissions [14]. Additionally, they significantly contribute to ADRs, with approximately 3% to 26% of drug interaction-related ADRs requiring hospitalization [15]. Research conducted by Santos and colleagues indicates that DDIs account for 17% of all preventable adverse drug events among hospitalized patients [16]. A systematic review of 34 prospective studies also reported that DDIs were the most common drug-related problem in hospitalized patients [17].

The pDDIs prevalence in diabetes patients varies across different studies. Research conducted in tertiary care outpatient settings reports a prevalence rate ranging from 50% to 75% [18,19]. Another study conducted among diabetes patients across six different hospitals in Jordan found a high prevalence of 96% of pDDIs. According to this study, diuretics are the most common class of drugs involved in interactions [20]. This relatively high prevalence of DDIs is primarily attributed to polypharmacy involved in the management of this condition. It increases morbidity and mortality, prolongs hospital stays, and elevates healthcare expenses [21]. These findings highlight the importance of detecting and managing pDDIs to improve patient safety and reduce the incidence of adverse events associated with medication use [22]. The additional burden and consequences of harmful DDIs in diabetes patients are preventable because of their predictable nature [23]. Various software tools are available to detect pDDIs, including Lexi-Interact, Micromedex, Medscape, Epocrates, Harmavista, and Stockley's Drug interactions [24].

Although the prevalence and associated factors of pDDIs have been widely studied, these studies have predominantly focused on outpatient settings and non-specific patient groups. However, DDIs in hospitalized diabetic patients remain a gray area with many contradictions. With this in mind, our study aims to determine the prevalence, severity, common interacting pairs, and factors associated with pDDIs among diabetes patients in inpatient settings at Universitas Indonesia Hospital.

Methods

Study Design and Setting

A retrospective cross-sectional study was conducted on the inpatients of Universitas Indonesia Hospital (RSUI), a large general hospital that integrates medical service, education, and research.

Patient Selection Criteria

Patients diagnosed with diabetes and hospitalized during the 1-year period (from 01 January 2023 to 31 December 2023), aged over 20 years, who used at least two prescribed medications during their hospital stay, regardless of gender, were eligible for this study.

A total of 2453 patients were hospitalized during the study period. 2139 patients were excluded (non-diabetics), n=23, admitted to ICU: n=15; patients are prediabetes and on diet restrictions: n=4; age below 20 years; n=73, patients with incomplete medical record. In total, 200 patients met the inclusion criteria of the study.

Administrative and Ethical Approval

Administrative permission was obtained from the hospital to access patients' electronic medical records. Ethical approval was obtained from the ethical committee board of the Universitas Indonesia Hospital (S-025/KETLIT/RSUI//II/2024). As the study relied solely on medical records, obtaining Individual informed consent was not applicable.

Data Source

We searched and screened these records for age, gender, hospital stay, diagnosis, and comorbidities for all patients to minimize selection bias. Patients who met the inclusion criteria were selected using a consecutive sampling technique. Following this, the prescribed medicine and dosage regimen were recorded from the patient's daily progress sheets in their files. This approach ensured a systematic and comprehensive inclusion of relevant cases for our study.

Screening for pDDIs

Medicines prescribed to patients were screened for pDDIs using Lexi-Interact™ in UpToDate [25]. This software classifies drug interaction on the basis of severity: (major, moderate, and minor), risk rating (X (avoid combination), D (consider therapy modification), C (monitor therapy), B (no action needed), A (no known interaction)) and documentation-level (excellent, good, fair and poor) [25]. Several past studies evaluated the

performance of Lexi-interact and recognized it as a high-drug screening software. In most of these studies, Lexi-interact was found to be highly specific (80-90%) and sensitive (87-90%) software [26–28].

The overall prevalence of pDDIs, defined as the presence of at least one pDDI in a patient prescription, and the prevalence based on severity, risk rating, and documentation levels were reported. A list of the most frequent (widespread) pDDIs was provided. The list also includes the potential impact on clinical outcomes and the level (severity, risk rating, and documentation) of such pDDIs.

Statistical Analysis

The collected data were analyzed using Statistical Package for the Social Sciences (SPSS) version 27, (Armonk, New York, USA). Descriptive statistics were used to present data as frequency and percentages across all variables examined. Median values and interquartile ranges (IQR) were also reported where applicable. A statistical method of logistic regression analysis was utilized to assess the likelihood of risk factors contributing to pDDIs. These risk factors included the patient's gender, age, total number of medications prescribed, duration of the hospital stay, and number of comorbid conditions. For each predictor, odds ratios and 95% confidence intervals (CIs) were calculated. The approach began with univariate logistic regression and then moved to multivariate analysis for variables with p-values of ≤0.05. A p-value of 0.05 or less was set as the threshold for statistical significance.

Result and Discussion

During the study period, out of 200 patients, males were slightly more prevalent (50.5%) and aged 45 years or older, with a median age of 60, as shown in Table 1. These findings correlated with their proportion with research conducted by Roosyidah et al., which found that diabetes is more prevalent in older adult males [29]. The increased exposure to diabetes in this demographic is attributed to complex and interrelated factors. Biologically, aging in males is associated with a significant reduction in testosterone levels, which regulates insulin sensitivity and body fat distribution factors, directly impacting glucose

Table 1. General characteristics of study patients and exposure to all pDDIs and major pDDIs (n = 200).

Characteristics	Patients: n (%)	Exposure to pDDIs (patients n: (%)	
		All types of pDDIs	Major-pDDIs
Gender			
Male	101 (50.5%)	87 (48.9%)	24 (42.1%)
Female	99 (49.5%)	91 (51.1%)	33 (57.9%)
Age (Years)			
20-45	20 (10%)	17 (9.6%)	3 (5.3%)
>45	180 (90%)	161(90.4%)	54 (94.7%)
Median (IQR)	60 (52-69)		
Drugs are prescribed per patient.			
≤4	23 (11.5%)	7 (4%)	0 (0%)
5-8	45 (22.5%)	41 (23%)	4 (7%)
>8	132 (66.0%)	130 (73%)	53 (93%)
Median (IQR)	10 (7-13)		
Number of Comorbidities			
≤2	116 (58.0%)	95 (53.4%)	15 (26.3%)
≥3	84 (42.0%)	83(46.6%)	42 (73.7%)
Median (IQR)	3 (2-5)		
Hospital stays(days)			
≤1	29 (14.5%)	18 (10.1%)	2 (3.5%)
2≥	171 (85.5%)	160 (89.9%)	55 (96.5%)
Median (interquartile range)	3 (2-5)		

IQR, interquartile range.

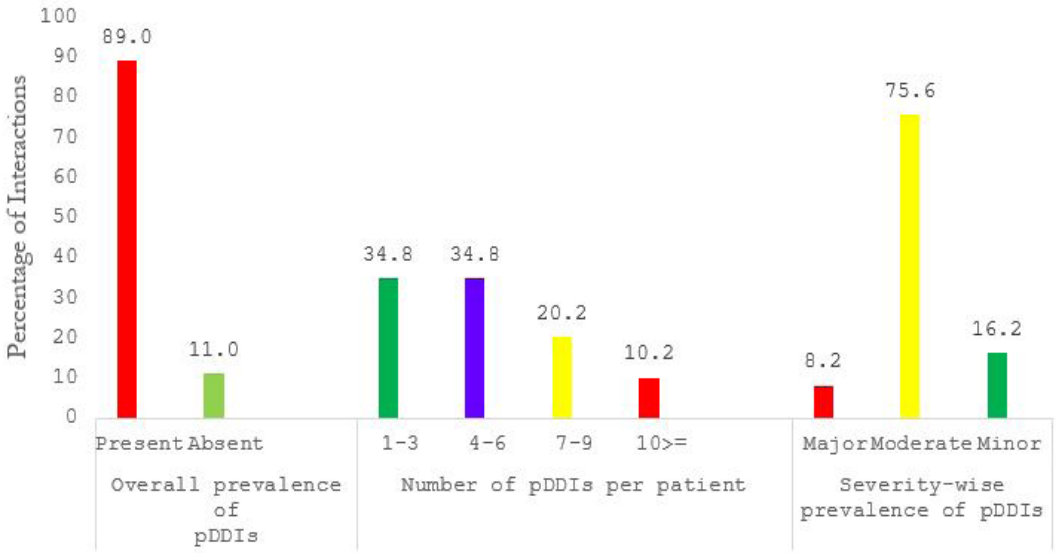

Figure 1. Prevalence of potential drug drug interactions.

metabolism [30]. Furthermore, (66%) of patients were prescribed eight or more medications with a median of 10 medicines (IQR 7–13). This indicates a high level of polypharmacy, consistent with the findings of other research among similar population groups [31,32].

Additionally, our results showed that most patients (85.5%) stayed in the hospital for two or more days, with a median stay of 3 days (IQR 2-5). Moreover, 58% of patients had two or fewer comorbidities, with a median of 2 (IQR 2–3). Consequently, our findings on hospital stays and comorbidities can be contrasted with those from a recent study conducted on diabetic foot ulcer patients in Romania, which showed markedly different results [33]. This discrepancy in results may be due to different healthcare setups and regional disparities between the populations studied.

Table 1 also shows exposure to all types of pDDIs and major pDDs stratified by patients' characteristics. In females, the incidence of pDDIs of all types and major severity was more frequent as compared to males. Similarly, all types of pDDIs and major pDDIs were more frequently observed in patients aged >45 years, taking >8 medicines, and a hospital stay of 2≥ days. While in patients with ≤2 comorbidities showed a higher prevalence of all types of pDDIs, whereas those with ≥3 comorbidities exhibited a higher frequency of major pDDIs. A similar

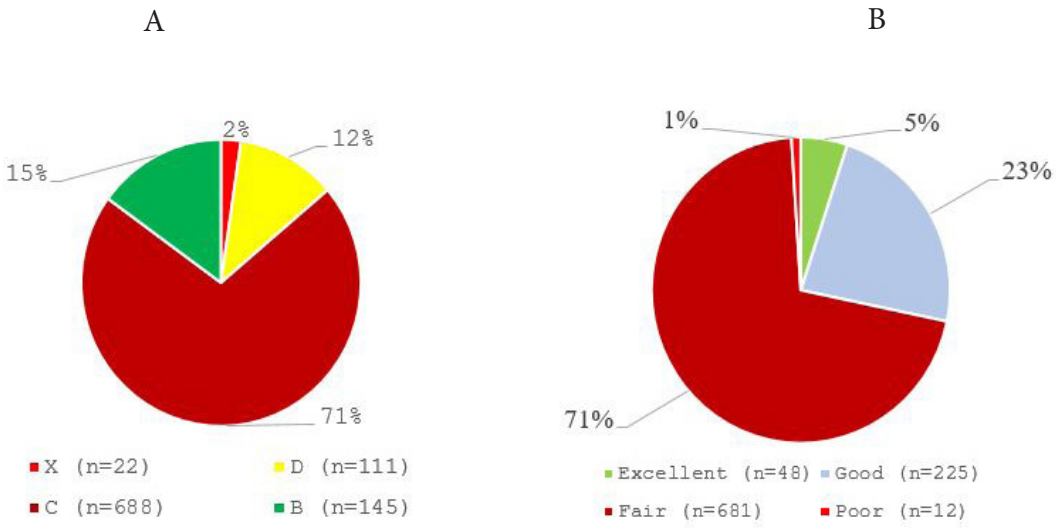

Figure 2. A Risk rating of pDDIs. B Reliability rating of pDDIs.

Table 2. Logistic regression model for factors associated with potential drug-drug interactions among 200 admitted Universitas Indonesia Hospitals.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender				
Female	Reference			
Male	1.2(0.5-3.1)	0.6	-	-
Age (years)				
≤45	Reference			
≥45	1.5(0.4- 5.8)	0.5	-	-
Drugs prescribed per patient				
≤4	Reference		Reference	
5-8	23.4(6.0-91.0)	<0.001	22.8(5.5-94.7)	<0.001
>8	148.6(28.4-777.5)	<0.001	64.4(11.3-366.5)	<0.001
Number of comorbidities				
≤2	Reference		Reference	
≥3	18.3(2.4-139.4)	0.005	7.5(0.7-76.4)	0.08
Hospital stays (days)			.	
≤1	Reference		Reference	
2≥	8.9(3.4-23.9)	<0.001	2.8(0.7-10.8)	0.1

CI confidence interval, OR odds ratio

observation was reported in a cohort study conducted among hospitalized hepatitis patients in Pakistan [34]. Regardless of their different primary diseases, both groups of patients experience similar challenges, such as polypharmacy, complexity of multiple comorbidities and prolonged hospital stay.

Figure 1 illustrates that out of 200 diabetic patients, 178 (89%) had at least one pDDIs while 22 patients (11%) had no interaction. In this current study of diabetes patients, the incidence of prescriptions with pDDIs is slightly lower than the findings reported by the Iranian study, whereas 91.43% of prescriptions showed pDDIs. Consequently, the Iranian research was conducted in an intensive care unit where patients have more critical health conditions and receive multiple concurrent treatments [35]. Another study from India reported a prevalence of 70% of pDDIs among diabetes patients [36]. This is lower than the current study's findings and could be related to the small sample size, which may not adequately represent the full range of drug interactions in the diabetes patient population.

A total of 966 pDDIs were recorded. Based on severity-wise prevalence, moderate and minor pDDIs were identified in 731 (75.5%) and 156 (16.2%), respectively. However, the lowest prevalence was recorded for major pDDIs, 79 (8.2%), as presented in Figure 1. Furthermore, in the current study, the prevalence of major interactions is markedly lower as compared to the study among hospitalized cardiac patients (52.6%) [37], malaria (46%) [38], malignancy (31.2%) [39], and chronic kidney disease (12.5%) [40]. In contrast, it is higher in comparison to that reported among in-patients with hypertension (4.4%) [41]. Moreover, the prevalence of moderate interaction aligns with the study conducted on geriatric diabetes patients (75%) [42]. However, in studies conducted elsewhere, the frequency of moderate interaction is lower than our findings [43]. This contradiction may be due to the diverse approaches used to identify and classify pDDIs.

Figure 2[a,b]. illustrates the categorization of pDDIs based on risk and reliability ratings, which is crucial for monitoring and managing adverse events related to interaction**.** Among the 966 pDDIs identified,

Table 3. Most frequently interacting pairs and their prevalence, risk rating, severity, reliability rating, and predicted impact on the clinical outcome.

Interacting pairs	Prevalence (%)[a]	Risk rating	Severity Level	Reliability rating	Predicted impact on the clinical outcome
Metformin+ Ondansetron	18(2%)	C	Moderate	Good	Ondansetron increases plasma concentrations of Metformin
Atorvastatin + Amlodipine	16(1.5%)	B	Minor	Fair	Amlodipine Increased the serum concentration of
Metformin + Bisoprolol	11(1.1%)	C	Moderate	Good	Beta-blockers may enhance the hypoglycemic effect of metformin.
Clopidogrel + Omeprazole	10(1.0%)	D	Major	Good	Omeprazole significantly diminishes the antiplatelet effect of Clopidogrel.
Novo rapid insulin + Metformin	7(0.7%)	C	Moderate	Fair	Hypoglycemia
Glimepiride + Levofloxacin	6(0.6%)	C	Moderate	Fair	Hypoglycemia or hyperglycemia
Gliclazide + omeprazole	5(0.5%)	C	Moderate	Good	Hypoglycemia

[a] The percentage was calculated of 966 interactions, i-e., the total number of interactions

n=688 were in risk category C, n=145 in risk category B, n=111 were in risk category D, and n=22 in risk category X. Whereas concerning scientific evidence, fair reliability ratings were associated with n=681, and good reliability rating of n=225 were mostly observed pDDIs. Our results are in line with the research of a study conducted among outpatients [44]. Similarly, studies among hospitalized patients show consistent results [45–47]. These results suggest that most potential DDIs (risk rating =C) require no significant clinical measures but close monitoring and proper follow-up for any adverse events. The risk associated with Category D requires intensive monitoring and sometimes modification of therapy due to the risk of severe adverse clinical outcomes. The majority of category X potential DDIs are severe and have a high risk of mortality if not identified and managed appropriately.

Table 2 shows the factors associated with exposure to pDDIs based on logistic regression analysis. The results of univariate logistic regression showed that patients who were prescribed 5-8 medications (OR=23.4, 95% CI=6-91, p- <0.001) and above eight medications (OR=148.6, 95% CI=28.4- 777.5, p- <0.001) had a higher risk of exposure to pDDIs. Also, univariate analysis revealed that the odds of pDDIs were higher when the patient had three or more comorbid conditions (OR=18.3, 95% CI=2.4-139.4, p=0.005). Moreover, the odds of exposure to pDDIs were higher for a hospital stay of ≥2 days (OR=8.9, 95% CI=3.4-23.9, p<0.001) as compared to ≤1 days. Furthermore, the univariate analysis found no significant association with gender or age.

In multivariate logistic regression analysis, the association of pDDIs remained significant with 5–8 prescribed medicines (OR=22.8; 95% CI=5.5-94.7; p<0.001), >8 prescribed medicines (OR=64.4; 95% CI=11.3-336.5; p<0.001) also shown in Table 2**.** In the current study, polypharmacy is identified as a factor associated with the occurrence of pDDIs, which is in line with the results conducted by Anfinogenova et al. [48]. Several studies have drawn the same conclusion that an increase in the number of medications was a risk factor for DDIs [49–51].

Based on Table 3. Metformin + Ondansetron and Atorvastatin + Amlodipine were identified as common interacting pairs, with a prevalence of 18(2%) and 16(1.5%), respectively and followed by Metformin +Bisoprolol and Clopidogrel + Omeprazole which showed prevalence of 11(1.1%) and 10(1.0%). Several studies investigated the most common interaction pairs and reported different results. In studies conducted in KSA [52], Australia [53], and India [54], the most common interacting pairs were metformin and aspirin. In a study conducted in Uganda, the most common interacting pair is Metformin + Quinine [44]. The discrepancy observed in the most common interacting pairs is due to treating specific conditions, medication availability, and the different healthcare practices of each institute. Healthcare

professionals can manage these potential DDIs by enhancing the medication review protocols to assess the patient's medications for potential interactions. This will help in maximizing the risk of pDDIs. In this study, the predicted impact on the clinical outcome of the most frequent pDDIs were hypoglycemia, hyperglycemia**,** and a reduction in therapeutic effectiveness**.** These findings are somehow aligned with a study on ICU patients, in which most prevalent potential adverse outcomes due to pDDIs were hypoglycemia, hyperglycemia, and hyperkalemia [33].

Strengths and Limitations

This is the first study to focus on the prevalence and predictors of pDDIs in hospitalized diabetic patients in Indonesia. The research shows the significant risks that multiple medication regimes pose in these vulnerable populations. It also underscores the need for careful medication management and monitoring, offering practical implications for enhancing patient care and safety. However, we also encountered certain limitations in this study. First, this was a single-center study conducted in relatively urban areas. Therefore, the study may not accurately extend to a country as extensive and diverse as Indonesia. A multicenter survey may be needed to understand the extent of pDDIs in diabetes patients. Second, the soul of this study is the Lexicomp drug interaction checker tool. Although Lexicomp is a popular tool for drug interaction among healthcare professionals, some drugs were (herbal products) not listed in Lexicomp but prescribed to the patients.

Conclusion

Our study revealed a very high prevalence of pDDIs among hospitalized diabetic patients, with most interactions being moderate in severity and having a fair reliability rating. However, there were also a considerable number of major pDDIs. The most common drug-interacting pairs were metformin + ondansetron and atorvastatin + amlodipine. The number of drugs taken during hospital stays is a significant factor associated with pDDIs. These findings highlight the need for careful medication management and monitoring to improve patient safety and outcomes. Appropriate strategies should be implemented to reduce the risk of pDDIs.

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