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Polypharmacy and Potential Drug Interactions in Hospitalised Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a prevalent chronic disease often accompanied by comorbidities that require multiple medications, increasing the risk of potential drug interactions. This study analysed the association between polypharmacy and potential drug interactions in hospitalised patients with type 2 diabetes mellitus at Kramat Jati Regional General Hospital. A retrospective cross-sectional study was conducted using medical records of 94 inpatients from October to December 2024. Potential drug interactions and their severity were assessed using Drugs.com, and statistical analysis was performed with the Chi-square test. Results showed that 93 patients (98.8%) experienced potential drug interactions, predominantly of moderate severity (82.5%). The most frequent interaction was between metformin and ranitidine. A significant association was observed between polypharmacy and potential drug interactions (p = 0.002). These findings highlight the importance of early detection and management of drug interactions in type 2 diabetes mellitus inpatients, with clinical pharmacists playing a crucial role in optimising therapy safety.

Keywords
Type 2 Diabetes Mellitus; Polypharmacy; Drug Interaction; Hospitalised Patients; Retrospective Study

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1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterised by chronic hyperglycaemia due to impaired insulin secretion, impaired insulin response, or both [1]. It remains a major global health concern, with prevalence continuing to rise annually. Southeast Asia ranks third globally for DM cases, and Indonesia is sixth among the ten Asian countries with the highest prevalence [2]. According to the International Diabetes Federation (IDF), in 2023 there were approximately 540 million individuals living with diabetes, with a projected increase in the coming years [3]. Based on the 2023 Indonesian Health Survey (SKI), the prevalence of DM in Indonesia based on a doctor's diagnosis is 1.7% of the total population and 2.2% of those aged ≥15 years, with the highest rates reported in Jakarta Special Capital Region, Yogyakarta Special Region, and East Kalimantan [4].

As the disease progresses, patients with DM often develop comorbidities that necessitate multiple medications. This widespread use of medications, known as polypharmacy, significantly increases the risk of drug interactions, particularly in

hospitalised patients who typically present with more severe disease conditions and multiple complications. A study published in *Frontiers in Endocrinology* emphasises that polypharmacy is highly prevalent among hospitalised type 2 DM patients due to multimorbidity, making the assessment of potential drug interactions essential for ensuring safe and rational therapy [5].

Drug interactions occur when the pharmacological effect of a drug is altered by another drug, food, herbal product, or environmental chemical change, potentially increasing toxicity or reducing efficacy. They are categorised as minor, moderate, or major based on clinical significance [6]. Identifying and managing these interactions is critical, as moderate-to-severe interactions can lead to adverse outcomes requiring hospitalisation.

Previous research at Rama Hadi General Hospital in Purwakarta found a significant association between polypharmacy and potential drug interactions in type 2 DM patients, with a p-value of 0.001 [7]. However, there is limited evidence focusing specifically on inpatients with type 2 DM in Indonesia. Therefore, this study aims to evaluate the relationship between polypharmacy and potential drug interactions among hospitalised type 2 DM patients at Kramat Jati Regional General Hospital during October–December 2024.

2. Method

Study Design and Setting

This study employed an analytical cross-sectional design with a retrospective approach. The research was conducted at Kramat Jati Regional General Hospital from October to December 2024.

Study Population and Sampling

The study population included all inpatients diagnosed with type 2 diabetes mellitus (T2DM) during the study period. A total sampling technique was applied, resulting in 94 eligible patients.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) patients aged ≥20 years; (2) confirmed diagnosis of T2DM by a physician; (3) hospitalisation during the study period; and (4) complete medical and medication records. Exclusion criteria were: (1) incomplete medical records and (2) use of medications not listed in the hospital formulary.

Data Collection

Data were obtained from patients' medical records and medication therapy lists. Potential drug interactions and their severity were assessed using *Drugs.com* clinical interaction checker [6]. The severity was classified into three categories: minor, moderate, and major [6].

Data Analysis

Data analysis was performed using SPSS version 25. Descriptive statistics were used to determine the distribution of drug interactions and severity levels. The Chi-square test was applied to evaluate the association between polypharmacy and potential drug interactions, with a significance threshold of $p < 0.05$ [7].

Ethical Approval

The study protocol was approved by the Research Ethics Committee of STIKes IKIFA, Jakarta, Indonesia (Approval No. 000704/Komite Etik Penelitian STIKes IKIFA/2025; approval date: 12 March 2025), in compliance with the WHO 2011 Standards and the 2016 CIOMS Guidelines.

3. Results and Discussion

Incidence of Drug Interactions

Polypharmacy is a well-recognised factor contributing to the high rate of potential drug interactions, particularly in hospitalised patients with type 2 diabetes mellitus (T2DM), who often present with multiple comorbidities and require complex therapeutic regimens. Identifying the incidence of these interactions is an important first step in assessing patient safety risks and designing targeted interventions. In this study, the distribution of potential drug interactions among T2DM inpatients was evaluated based on medication records and assessed using *Drugs.com*.

Table 1. Percentage of Potential Drug Interaction Events

No	Drug Interaction	Number of Patients (n)	Percentage (%)
1	There is an interaction	93	98
2	No interaction	1	1.10
	Total	94	100

As shown in **Table 1**, the vast majority of hospitalised T2DM patients (98.8%) experienced at least one potential drug interaction, while only one patient (1.1%) had no recorded interaction. This proportion is strikingly similar to the prevalence reported at Sultan Agung Islamic Hospital, Semarang, where 47 of 51 inpatients (92.2%) demonstrated at least one potential interaction [8].

The extremely high incidence in this study can be attributed to the complexity of T2DM management in hospitalised settings, where patients often present with multiple comorbidities and require combination pharmacotherapy. As the number of prescribed medications increases, the likelihood of potential drug interactions rises significantly. A systematic review reported that the probability of drug interactions escalates from approximately 4% in patients prescribed fewer than five medications to as high as 54% in those receiving more than five [9].

This finding underscores the necessity of routine drug interaction screening in inpatient settings, particularly for populations with high comorbidity burdens such as T2DM. Early identification enables the implementation of targeted interventions, including medication review and optimisation by clinical pharmacists, to reduce the risk of adverse drug events.

Severity of Potential Drug Interactions

In addition to determining the incidence, classifying potential drug interactions by severity is essential for prioritising clinical interventions. The severity classification provides insight into the potential clinical impact of each interaction, guiding healthcare professionals in deciding whether to continue, adjust, or discontinue a therapy. In this study, severity was categorised into minor, moderate, and major interactions based on the *Drugs.com* clinical interaction checker [6].

Table 2. Severity of Potential Drug Interactions

No	Type of Interaction	Number of Interactions (n)	Percentage (%)
1	Minor	85	6.8
2	Moderate	1030	82.5
3	Major	134	10.7
Total		1249	100

As shown in **Table 2**, the majority of identified interactions were of moderate severity (82.5%), followed by major (10.7%) and minor (6.8%). This distribution is consistent with findings from a study in South Tangerang, where moderate interactions accounted for 89.4% of cases among T2DM inpatients [10].

Moderate interactions, while not immediately life-threatening, can cause significant clinical consequences if not addressed, particularly in patients with multiple comorbidities and complex medication regimens [11]. Such interactions may necessitate closer monitoring, dose adjustments, or substitution with safer alternatives. Major interactions, though less frequent, require immediate attention due to their potential to cause severe adverse effects or therapeutic failure.

Given that more than four-fifths of all detected interactions in this study were of moderate severity, continuous monitoring and proactive pharmacist involvement are warranted to prevent progression to clinically significant harm.

Most Common Drug Interaction Pairs

Identifying the most frequent drug interaction pairs is important for prioritising monitoring and prevention strategies in clinical practice. By recognising high-risk combinations, healthcare professionals particularly clinical pharmacists can implement targeted interventions to reduce adverse outcomes. In this study, the top 10 most frequent drug interaction pairs were identified from the medication records of hospitalised T2DM patients, with severity classification based on the *Drugs.com* database [6].

Table 3. Top 10 Most Frequent Drug Interaction Pairs

No	Drug A	Drug B	Frequency (n)	Severity
1	Ranitidine	Metformin	32	Moderate
2	Insulin	Metformin	27	Moderate
3	Glimepiride	Apidra Solostar	19	Moderate
4	Metformin	Apidra Solostar	17	Moderate
5	Insulin	Candesartan	12	Moderate
6	Ranitidine	Glimepiride	11	Moderate
7	Ketorolac	Metformin	11	Moderate
8	Insulin	Glimepiride	10	Moderate
9	Ibuprofen	Metformin	10	Moderate
10	Combivent	Metformin	10	Moderate

As shown in **Table 3**, the most frequent interaction was between ranitidine and metformin (32 cases), classified as moderate in severity. This combination is clinically significant because metformin is eliminated unchanged via renal excretion, and ranitidine can inhibit the Multidrug and Toxin Extruder 1 (MATE1) transporter in the kidneys, thereby reducing metformin clearance [12]. Reduced clearance increases plasma concentrations of metformin, which under certain conditions may raise the risk

of metformin-associated lactic acidosis (MALA), a rare but potentially fatal adverse effect.

Several other frequent pairs, such as insulin–metformin and glimepiride–Apidra Solostar, also carry the risk of altered glycaemic control due to additive hypoglycaemic effects. These findings highlight the necessity for routine screening of medication regimens, especially when prescribing combinations involving metformin, sulfonylureas, or insulin in hospitalised T2DM patients.

Association Between Polypharmacy and Potential Drug Interactions

Polypharmacy, generally defined as the concurrent use of five or more medications, is a known risk factor for drug–drug interactions (DDIs). In patients with type 2 diabetes mellitus (T2DM), the need to manage multiple comorbidities often leads to extensive medication regimens, thereby increasing the likelihood of DDIs [13],[14]. Evaluating the statistical association between the number of medications and the occurrence of potential drug interactions is critical for understanding the scope of the problem and informing intervention strategies.

Table 4. Association Between Polypharmacy and Potential Drug Interactions

Number of Medications	Interaction Present (n)	No Interaction (n)	Total (n)	p-value
5–10	5	1	6	
11–15	38	0	38	0.002
16–20	36	0	36	
>20	14	0	14	
Total	93	1	94	

As presented in **Table 4**, the Chi-square test revealed a statistically significant association between polypharmacy and potential drug interactions ($p = 0.002$). This finding aligns with previous research at Rama Hadi General Hospital, Purwakarta, which reported a similar significant association ($p = 0.001$) [7]. The consistency of these results across different institutions suggests that the relationship between polypharmacy and DDIs is generalisable to the wider inpatient T2DM population.

The results also indicate a clear dose–response trend: as the number of prescribed medications increases, so does the incidence of potential drug interactions, reaching 100% among patients receiving more than 10 medications. This is consistent with evidence showing that T2DM patients taking ≥8 drugs have a markedly increased likelihood of experiencing multiple DDIs, which can contribute to prolonged hospital stays, higher treatment costs, and worse clinical outcomes [5].

These findings underscore the need for integrated strategies—such as regular medication reviews, the application of clinical decision support tools, and active pharmacist involvement—to mitigate the risks associated with polypharmacy in hospitalised T2DM patients.

Clinical Implications

The findings of this study highlight the urgent need for systematic risk assessment of potential drug–drug interactions (DDIs) in hospitalised patients with type 2 diabetes mellitus (T2DM), particularly given that most interactions identified were of moderate severity. Although moderate interactions are not immediately life-threatening,

they can still lead to significant therapeutic complications if not addressed, especially in patients with multiple comorbidities and complex medication regimens [11].

Polypharmacy in T2DM inpatients has been associated with prolonged hospital stays, poorer glycaemic control, an increased incidence of adverse drug reactions, and higher healthcare costs [14]. In this context, clinical pharmacists have a pivotal role in optimising medication safety through early identification of high-risk drug combinations at the point of hospital admission, comprehensive therapeutic regimen reviews to adjust dosages or substitute safer alternatives, and continuous monitoring for early signs of clinically significant interactions. Equally important is patient and caregiver education to raise awareness about potential interaction risks and the need for strict adherence to prescribed therapy. Furthermore, integrating clinical decision support systems—such as *Drugs.com* and Lexicomp—into hospital workflows can provide automated alerts that facilitate timely detection and management of DDIs. Evidence from previous studies demonstrates that such structured pharmacist-led interventions can significantly reduce the occurrence of drug-related problems in T2DM patients, thereby improving treatment outcomes and reducing preventable adverse events [15].

This study has several limitations that should be considered when interpreting the results. First, the retrospective design relied solely on secondary data from medical records, which may be incomplete or lack important clinical details such as laboratory parameters or patient-reported adverse events. Second, the analysis focused exclusively on identifying potential drug–drug interactions (DDIs) based on database screening using *Drugs.com*, without confirming whether these interactions resulted in actual clinical manifestations. As a result, the findings represent the potential risk rather than the observed clinical impact of DDIs. Third, the study was conducted in a single hospital setting over a relatively short three-month period, which may limit the generalisability of the results to other healthcare institutions or populations. Finally, the classification of interaction severity was based on a single reference source, which could introduce classification bias; incorporating multiple drug interaction databases in future research may provide a more comprehensive assessment [6],[7]. Future studies with a prospective design, larger sample sizes, and clinical outcome monitoring are recommended to validate these findings and assess the real-world consequences of DDIs in hospitalised patients with type 2 diabetes mellitus

4. Conclusion

This study demonstrated a statistically significant association between polypharmacy and the occurrence of potential drug–drug interactions (DDIs) in hospitalised patients with type 2 diabetes mellitus (T2DM) at Kramat Jati Regional General Hospital, with a prevalence rate of 98.8% and the majority of interactions classified as moderate in severity. The most frequent interaction was observed between metformin and ranitidine, a combination with the potential to increase systemic exposure to metformin and elevate the risk of metformin-associated lactic acidosis. These findings underscore the urgent need for systematic DDI screening in inpatient settings, particularly for patients with complex comorbidities requiring multiple medications. The integration of clinical pharmacists into the multidisciplinary care team, along with the use of electronic clinical decision support systems, is strongly recommended to identify, monitor, and manage potential interactions effectively. Future research should employ prospective designs to assess the actual clinical impact of DDIs and to evaluate the effectiveness of targeted pharmacist-led interventions in

reducing adverse outcomes.

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Conflicts of Interest:

The authors declare no conflicts of interest in relation to the design, implementation, or publication of this study.

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