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SCREENING OF POTENTIAL DRUG-DRUG INTERACTIONS AMONG GERIATRIC PATIENTS POST-CARDIAC SURGERY: INSIGHTS FROM MICROMEDEX AND LEXIDRUG

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Abstract

Background: *The global increase in the ageing population has heightened the Prevalence of cardiovascular diseases (CVD), particularly in Pakistan. Older patients, especially those undergoing cardiac surgery, are at significant risk for polypharmacy and potential drug-drug interactions (pDDIs), which can lead to adverse clinical outcomes. However, the Prevalence of pDDIs in geriatric cardiac surgery patients has not been thoroughly explored in Pakistan.*

Objective: *This study is designed to evaluate the Prevalence, severity, and types of pDDIs in geriatric patients post-cardiac surgery, utilizing two widely used drug interaction databases, Micromedex and Lexidrug. The study further explored the relationship between polypharmacy and the Prevalence of pDDIs.*

Methods: *An observational study was conducted on 96 geriatric patients (age ≥ 60 years) who underwent cardiac surgery at a tertiary care hospital in Pakistan. Sociodemographic and clinical data were collected, including information on comorbidities, surgical procedures, and prescribed medications. pDDIs were screened using Micromedex and Lexidrug databases, which categorize interactions by severity, onset, and documented evidence (Micromedex) or risk ratings (Lexidrug). Statistical analysis was performed to assess associations between polypharmacy and pDDIs.*

Results: *The study revealed a high prevalence of pDDIs, with 98.5% and 100% of patients having at least one interaction identified by Micromedex and Lexidrug, respectively. Most pDDIs were classified as major (66.4% by Micromedex and 61.5% by Lexidrug). A significant association was found between the prescribed drugs and the Prevalence of pDDIs, with polypharmacy (≥11 drugs) significantly increasing the risk of interactions. Commonly identified high-risk drug pairs*

included aspirin-clopidogrel, aspirin-furosemide, and clopidogrel-omeprazole.

Conclusions: *This study reveals a high prevalence of pDDIs in geriatric cardiac surgery patients, with 98.5% and 100% identified by Micromedex and Lexidrug, respectively. Most interactions were classified as major, with polypharmacy strongly linked to increased pDDIs. High-risk drug combinations, such as aspirin and clopidogrel, were common. These findings emphasize the need for practical drug-drug interaction screening tools to improve medication safety, particularly in resource-limited settings.*

INTRODUCTION

The global ageing population is projected to grow rapidly, from 9% to 16% between 2019 and 2050 (Adem & Tegegne, 2022). Advancing age is linked to a higher prevalence of comorbidities, disability, and polypharmacy (Fatemeh et al., 2021). Ageing impacts cardiac function by reducing the elasticity of the heart muscle and its capacity to adapt to variations in pressure (Strait & Lakatta, 2012). Consequently, it constitutes an independent risk factor for cardiovascular disease (CVD), placing a substantial burden on elderly individuals (Kane & Howlett, 2018). CVD was responsible for 32% of global deaths, with the majority (three-fourths) occurring in low- and middle-income nations. In Pakistan, the Prevalence of CVD is approximately 17.5%, contributing to 29% of total mortality (Zubair et al., 2018). Individuals with CVD face a heightened risk of pDDIs as a result of diverse etiological factors, the presence of multiple comorbidities, and the use of varied pharmacological treatments (Akbar et al., 2021a). pDDIs describe a patient's risk of encountering a potentially harmful combination of medications, as opposed to an actual occurrence of an adverse event (Van Leeuwen et al., 2013). Among drug-related problems, a pDDI is highly preventable, but it may lead to significant adverse outcomes or therapeutic failures (Ismail et al., 2018). Adverse pDDIs compromise treatment outcomes and are associated with elevated morbidity and mortality rates, as well as increased healthcare expenditures. (Murtaza, Khan, Azhar, Khan, & Khan, 2016). Earlier studies have reported the Prevalence of pDDIs in patients with CVD as varying between 21.3% and 96.9% (Akbar et al., 2021a).

The frequency, severity, and risk factors of potential drug-drug interactions (pDDIs) in cardiovascular disease (CVD) patients in Pakistan have been infrequently studied. Available research indicates a variable prevalence of pDDIs, with reported rates spanning from 42% to 96.5% (Ismail et al., 2012; Javaid et al., 2017). Research at Ayub Teaching Hospital in Pakistan identified that 91.6% of patients with CVD experienced at least one pDDI (Murtaza et al., 2016). A subsequent observational study identified a significant prevalence of pDDIs among postoperative CVD patients in Pakistan, with a notable proportion classified as major interactions. These results emphasize the importance of drug-drug interaction databases to detect and manage these risks, particularly in high-risk populations (A. U. Humza, Akbar, et al., 2024).

Despite the complexities and individual variations associated with drug-drug interactions, they are infrequently examined in clinical studies despite their significant clinical relevance. To prevent severe pDDIs and their associated side effects, it is essential to select medications with the lowest risk of such interactions (Low, Setia, & Lima, 2018). Studies have indicated that pDDIs can result in detrimental effects, such as hypoglycemia, nephrotoxicity, hyperglycemia, impaired platelet function, increased bleeding risk, hypokalemia, ECG changes, and postural hypotension. (Q. Khan, Ismail, Haider, Haq, & Noor, 2017; Mazhar, Akram, Haider, & Ahmed, 2016; Sankar, Saaed, Joseph, Azizi, & Mariyam Thomas, 2015). To minimize the risk of pDDIs, a clinical pharmacist needs to assess and manage the medication regimen thoroughly. (Ramalho de Oliveira, Brummel, & Miller, 2010). In such settings, a computerized drug-drug interaction screening tool is essential, as manual detection and identification of pDDIs is both time-consuming and labour-intensive. Consequently, interaction tools should be employed during the prescription and dispensing processes, with active intervention when necessary. (Moura,

Prado, Belo, & Acurcio, 2012; Taylor & Tamblyn, 2004).

Thus, This study intends to assess the Prevalence and types of pDDIs in geriatric patients following cardiac surgery using two widely used drug-drug interaction databases: Micromedex Drug-Int.® and Lexidrug®. By analyzing the relationship between polypharmacy and pDDIs, this research seeks to contribute valuable insights for optimizing medication management in geriatric care.

METHODS

Study Participants and Design

This retrospective observational study was conducted at a tertiary cardiac care hospital. A total of 96 geriatric patients (age ≥ 60 years) underwent cardiac surgery. The study received ethical clearance from the Ethical Review Committee (ERC) of the National Institute of Cardiovascular Diseases (NICVD).

Criteria (Inclusion and Exclusion)

Patients aged 60 years or older who were prescribed at least two medications, irrespective of the route of administration, were eligible for inclusion in the study. Patients younger than 60 years were excluded from the study.

Collection and Screening

Data collection included sociodemographic, clinical, and drug therapy information from the patient's medical charts, including primary diagnosis, comorbidities, type of surgery, and the list of prescribed medications, all recorded by their generic names. pDDIs were screened using Micromedex Drug-Int.®, and Lexidrug® (Abbas et al., 2022) was applied for screening pDDIs. Micromedex provides scientifically validated evidence on drug interactions, categorized by severity, onset, and documentation quality.

Severity levels:

- **Contraindicated**: Concurrent use is not recommended.
- **Major**: Life-threatening interactions requiring intervention.
- **Moderate**: Interactions that may worsen symptoms, requiring therapy adjustments.
- **Minor**: Limited clinical effects; no substantial therapy changes needed.

Documentation levels:

- **Excellent**: Supported by controlled research studies.
- **Good**: Based on strong evidence.
- **Fair**: Limited documentation, but clinical considerations strongly suggest interaction.

Onset of action:

- **Rapid**: Interactions occur within 24 hours.
- **Delayed**: Interactions observed after 24 hours.
- **Not Specified**: Onset duration not detailed in the literature (A. U. Humza, Akbar, et al., 2024).

Lexidrug® is a widely utilized, reliable, and targeted tool for screening pDDIs (Kheshti, Aalipour, & Namazi, 2016). Lexidrug® classifies interactions as:

A: No evidence of interaction
B: No further intervention is necessary
C: Continuous monitoring of therapy is recommended
D: Modification of therapy should be considered
X: Combination should be avoided due to excessive risk (Akbar et al., 2021a).

Each patient's medication therapy list was entered into both databases to generate reports on potential drug interactions.

Statistical Evaluation

The data were recorded in an MS Excel spreadsheet and reviewed for accuracy. Statistical analysis was conducted using IBM SPSS Statistics version 23.0. Continuous variables were analyzed through means, standard deviations, medians, and ranges, while categorical variables were evaluated using frequencies and percentages. The relationships between variables and pDDIs were examined, with a significance threshold set at $p < 0.05$ for all analyses.

RESULTS

Sociodemographic and Clinical Characteristics

The study included 96 geriatric patients post-cardiac surgery, with a mean age of 65.19 ± 4.09 years, ranging from 60 to 75 years. Of the participants, 72.9% (n=70) were male, and 27.1% (n=26) were female. The most common comorbidities included hypertension (HTN) and diabetes mellitus (DM)

(26%), and not-known comorbidity (NKCM) in 13.5%. In terms of surgical diagnoses, 70.8% (n=68) of patients had the three-vessel disease (3VD), and the most common surgical procedure was coronary artery bypass grafting (CABG), performed on 70.8% (n=68) of the patients (Table 1).

Polypharmacy and Prevalence of pDDIs

The average number of drugs prescribed was 10.5 ± 1.8, with 55.2% (n=53) of patients prescribed 11 or more medications. According to Micromedex, the majority of pDDIs identified were classified as major (66.4%), followed by moderate (31.9%) and minor (1.8%) interactions. The onset of the pDDIs was most frequently unspecified (61.2%), with rapid onset reported in 10.3% and delayed onset in 28.4%. In terms of documented evidence, the interactions were predominantly categorized as good (54.3%) or fair (28.3%) (Table 2).

Lexidrug identified a total of 96 pDDIs, with risk ratings of C (61.5%) being the most common, followed by B (21.8%), D (7.1%), and X (9.3%). Notably, no patients were identified with A-rated pDDIs (Table 2).

The study revealed a high prevalence of potential drug-drug interactions (pDDIs) among geriatric patients. The average number of pDDIs identified by Micromedex was 5.8 ± 2.7, ranging from 0 to 19. Lexidrug**,** on the other hand, identified an average of 6.6 ± 3.5 pDDIs per patient, ranging from 1 to 23. This suggests that Lexidrug detected a slightly higher frequency of pDDIs than Micromedex across the patient cohort (Table 2).

Association between polypharmacy and pDDIs

Table 4 presents the association between polypharmacy and pDDIs classified according to Micromedex and Lexidrug. A significant correlation was found between the number of drugs prescribed and the Prevalence of pDDIs. Specifically, patients prescribed 11 or more drugs exhibited a markedly higher prevalence of pDDIs compared to those prescribed fewer drugs (Micromedex: $p = 0.000$; Lexidrug: $p = 0.000$). Patients in the "≥11 Drugs" category had 20, 29, and 4 pDDIs identified by Micromedex, with corresponding numbers of 14, 29, and 10 for Lexidrug. This finding emphasizes the increased risk of pDDIs with polypharmacy in this population.

Major pDDIs and their Consequences

Table 3 outlines the most frequently identified drug pairs associated with major pDDIs as per Micromedex and Lexidrug. The most common drug pairs involved in major interactions included Aspirin - Furosemide (13.9%), **Aspirin - Clopidogrel** (12.3%), and Aspirin -Amiloride (11.9%), primarily due to pharmacokinetic and pharmacodynamic mechanisms. The potential consequences of these interactions included increased risk of bleeding (Aspirin-Clopidogrel, Aspirin-Warfarin), reduced diuretic effectiveness (Aspirin-Amiloride), and increased risk of salicylate toxicity (Aspirin-Furosemide).

Additionally, the interaction between **Clopidogrel and Omeprazole** (42 patients, 6.6%) was flagged as a significant concern in Micromedex and Lexidrug due to a pharmacokinetic mechanism resulting in decreased clopidogrel effectiveness. Other notable interactions include **Amiodarone - Domperidone** and **Ciprofloxacin - Warfarin**, leading to adverse effects like QT-interval prolongation and increased bleeding risks.

Comparative analysis of pDDIs identified by Micromedex and Lexidrug

Comparing the pDDIs identified by Micromedex and Lexidrug, a substantial overlap was observed, with both databases identifying high-risk interactions involving common drugs such as aspirin, clopidogrel, warfarin, and enoxaparin. However, the risk classification systems differed slightly, with Lexidrug providing more risk categorization (X, D, C, B, A), while Micromedex primarily focused on severity and onset. This suggests that the combined use of both databases provides a more comprehensive view of the potential drug interactions in this cohort.

DISCUSSION

This study evaluated the Prevalence and severity of pDDIs in geriatric patients following cardiac surgery, utilizing the Micromedex and Lexidrug databases. The findings underscore the high Prevalence of pDDIs among this population, which can significantly affect patient outcomes. The observed Prevalence of pDDIs in this cohort, particularly

concerning polypharmacy, aligns with previous research conducted in LMICs, including Pakistan, where similar studies have reported high rates of drug interactions in patients with CVD (A. U. Humza, Akbar, et al., 2024) .

The high Prevalence of pDDIs in the present study (98.5% and 100% as identified by Micromedex and Lexidrug, respectively) echoes findings from studies in Pakistan that documented a prevalence of pDDIs ranging from 42% to 96.5% in CVD patients. This high frequency can be attributed to the complex medication regimens often prescribed to geriatric patients post-cardiac surgery, who typically have multiple comorbidities requiring polypharmacy. Moreover, this study found polypharmacy was strongly associated with an increased risk of pDDIs, consistent with similar studies conducted in Pakistan (Akbar et al., 2021a; Ismail et al., 2018). These findings draw attention to the significant burden of pDDIs in postoperative CVD patients, underscoring the need for strategies to prevent their adverse consequences. CVD patients often present with multiple comorbidities, resulting in the use of various medications, which increases the risk of pDDIs. (A. U. Humza, Hameed, A., Akbar, M.A., Ahmed, I., Ali, A., Yousuf, J.B, 2024; M. Z. Khan, Sridhar, & Gupta, 2019).

The severity of the pDDIs was predominantly **major** (66.4%), according to Micromedex, which indicates that a significant proportion of these interactions could lead to severe clinical consequences such as bleeding, nephrotoxicity, and reduced drug effectiveness. These findings are in agreement with a study conducted in Pakistan that found a high proportion of major pDDIs in postoperative CVD patients. The association between major pDDIs and polypharmacy further emphasizes the need for vigilant monitoring and proactive drug management, especially in older adults who are more vulnerable to adverse effects from drug interactions (Akbar et al., 2021b).

In comparison, Lexidrug identified a high number of category **C** pDDIs (61.5%), suggesting that most interactions required therapy monitoring. However, category **X** interactions, which require the avoidance of drug combinations due to the associated risks, were identified in 9.3% of cases. This highlights the importance of utilizing a combination of tools like Micromedex and Lexidrug to comprehensively assess pDDIs, especially given the differences in risk classification across databases. In LMICs, where resources for detailed drug interaction screening may be limited, reliance on such tools can significantly enhance patient safety (Khaled, Almaghaslah, Nagib, Makki, & SHAFIQUE, 2023).

The interaction between **clopidogrel** and **omeprazole**, which was flagged in both databases, is particularly concerning due to its potential to reduce the effectiveness of clopidogrel, a crucial antiplatelet drug used in post-surgical care. This aligns with findings from other studies that emphasize the risks associated with this drug combination. These findings illuminate particular drug combinations that present a greater risk of interactions in postoperative CVD patients, enabling healthcare providers, especially clinical pharmacists, to direct their attention and take necessary actions to reduce potential harm. Moreover, electronic databases play a crucial role in identifying pDDIs and assist in making well-informed clinical decisions, including modifying treatment regimens or discontinuing drugs that may interact (Shakeel et al., 2018). The study revealed that medications extending the QTc-interval potentially increase the risk of QTc-interval prolongation (A. U. Humza, Siddiq, et al., 2024; Sánchez-López et al., 2016). Pharmacists are encouraged to improve their education and awareness regarding QTc-interval prolongation during drug reviews. Establishing pharmacist-driven QTc-interval monitoring is crucial for mitigating the risk of QTc-interval prolongation (A. U. Humza, Rizvi, & Ali, 2022).

The role of pharmacists is crucial in the management and monitoring of patients with pDDIs. With their specialized expertise, pharmacists can assess medication regimens, identify potential interactions, and recommend appropriate management strategies (Ahmed et al., 2021). Online drug-drug interaction screening tools, such as Micromedex Drug-Int® and Lexidrug®, are vital for pharmacists in identifying pDDIs. Pharmacists must advance their knowledge of pDDIs and collaborate in developing educational programs to improve patient counselling and prevent medication misuse. A detailed assessment of the patient's medication list should be conducted before evaluating the appropriateness of specific drug

combinations, thereby minimizing the likelihood of adverse interactions (A. U. Humza, Akbar, et al., 2024).

While the study provides important insights, several limitations should be acknowledged. First, this was a retrospective observational study conducted at a single tertiary care centre, which may limit the generalizability of the findings to broader populations in other regions of Pakistan or LMICs. Second, relying on two databases (Micromedex and Lexidrug) to detect pDDIs may not capture all possible interactions, particularly those rare or not included in these systems. Third, the study did not assess the clinical outcomes of the identified pDDIs, which would have provided a more comprehensive understanding of the real-world impact of these interactions. Future prospective studies incorporating clinical follow-up are needed to validate these findings and evaluate the effectiveness of intervention strategies to reduce pDDIs in geriatric cardiac surgery patients.

CONCLUSION

This study highlights the high Prevalence of pDDIs among geriatric patients following cardiac surgery, with 98.5% and 100% of patients experiencing pDDIs, as identified by Micromedex and Lexidrug, respectively. Most pDDIs identified were classified as major, underscoring their clinical significance and potential to compromise patient safety. These findings highlight the importance of utilizing drug interaction screening tools, especially in resource-limited settings like Pakistan, where polypharmacy is prevalent.

TABLES

Table 1: Sociodemographic and clinical characteristics of study participants (n=96)

Variables	**n(%) / Mean ± SD**
Gender	
Male	70 (72.9)
Female	26 (27.1)
Age (years)	
Mean ± SD	65.19 ± 4.09
Min - Max	60 - 75
Weight (Kg)	
Mean ± SD	65.5 ± 12.3
Min - Max	40 - 106
Comorbidities (Most Common)	
HTN, DM	25 (26.0)
HTN	22 (22.9)
NKCM	13 (13.5)
Diagnosis (Most Common)	
3VD	68 (70.8)
Post-CABG	9 (9.4)
Severe AS	3 (3.1)
Severe MR	3 (3.1)
Severe MS	3 (3.1)
Surgery (Most Common)	
CABG	68 (70.8)
Wound Debridement	9 (9.4)
MVR	6 (6.2)
AVR	3 (3.1)

Table 2: Polypharmacy & pDDIs Summary (n=96)

Variables	**n(%) / Mean ± SD**
Total Drugs prescribed	
Mean ± SD	10.5 ± 1.8
Min - Max	5 - 15
0-5 Drugs	1 (1.0)
6-10 Drugs	42 (43.8)
≥11 Drugs	53 (55.2)
Classification of pDDIs (Micromedex)	
Mean ± SD	5.8 ± 2.7
Min - Max	0 - 19
Severity	
Major	373 (66.4)
Moderate	179 (31.9)
Minor	10 (1.8)
Onset	
Rapid	58 (10.3)
Delayed	160 (28.4)
Not Specified	344 (61.2)
Documented Evidence	
Excellent	98 (17.4)
Good	305 (54.3)
Fair	159 (28.3)
Prevalence of pDDIs (Micromedex)	
Overall	95 (98.5)
None	1 (1.04)
Classification of pDDIs (Lexidrug)	
Mean ± SD	6.6 ± 3.5
Min - Max	1 - 23
Risk Rating	
X	59 (9.3)
D	45 (7.1)
C	392 (61.5)
B	139 (21.8)
A	2 (0.3)
Prevalence of pDDIs (Lexidrug)	
Overall	96 (100)
None	0 (0)

Table 3: The most frequently screened drug pairs involved in class (major) pDDIs (Micromedex) and (X, D) risk rating (Lexidrug) and their potential consequences (Micromedex)

Category	Drug interacting pair	n (%)	Mechanism of pDDIs	Potential Consequence
Major (Micromedex)	Aspirin - Furosemide	78 (13.9)	Pharmacokinetic	Increased risk of salicylate toxicity
	Aspirin - Clopidogrel	69 (12.3)	Pharmacodynamic	Increased risk of bleeding
	Aspirin - Amiloride	67 (11.9)	Pharmacokinetic	Reduced diuretic effectiveness
	Clopidogrel - Omeprazole	42 (7.5)	Pharmacokinetic	Decreased clopidogrel effectiveness
	Aspirin - Warfarin	14 (2.5)	Pharmacodynamic	Increased risk of bleeding
	Aspirin - Enoxaparin	13 (2.3)	Pharmacodynamic	Increased risk of bleeding
	Ceftazidim - Warfarin	9 (1.6)	Pharmacokinetic	Increased risk of bleeding
	Enoxaparin - Warfarin	8 (1.4)	Pharmacodynamic	Increased risk of bleeding
	Ciprofloxacin - Domperidone	7 (1.2)	Pharmacokinetic	QT-interval prolongation
	Amoxicillin - Warfarin	6 (1.1)	Pharmacokinetic	Increased risk of bleeding
	Clopidogrel - Enoxaparin	6 (1.1)	Pharmacodynamic	Increased risk of bleeding
	Amlodipine - Clopidogrel	6 (1.1)	Pharmacodynamic	Decreased antiplatelet effect
	Ciprofloxacin - Warfarin	3 (0.5)	Pharmacokinetic	Increased risk of bleeding
	Amlodipine - Domperidone	3 (0.5)	Pharmacokinetic	QT-interval prolongation
	Amiodarone - Warfarin	3 (0.5)	Pharmacokinetic	Increased risk of bleeding
	Amiloride - Enalapril	2 (0.4)	Pharmacodynamic	Hyperkalemia
X (Lexidrug)	Clopidogrel - Omeprazole	42 (6.6)	Pharmacokinetic	Decreased clopidogrel effectiveness
	Amiodarone - Domperidone	3 (0.5)	Pharmacokinetic	QT-interval prolongation
D (Lexidrug)	Aspirin - Enoxaparin	13 (2.0)	Pharmacodynamic	Increased risk of bleeding
	Aspirin - Warfarin	14 (2.2)	Pharmacodynamic	Increased risk of bleeding
	Clopidogrel - Enoxaparin	6 (0.9)	Pharmacodynamic	Increased risk of bleeding
	Amiodarone - Warfarin	3 (0.5)	Pharmacokinetic	Increased risk of bleeding

Table 4: Polypharmacy & pDDIs (Micromedex & Lexidrug)

Total Drugs with Micromedex pDDIs				
Total Drugs	**0-5 pDDIs**	**6-10 pDDIs**	**≥ 11 pDDIs**	**P-value**
≥ 11	20	29	4	0.000
0-5 Drugs	1	0	0	
6-10 Drugs	29	13	0	
Total Drugs with Lexidrug pDDIs				
Total Drugs	**0-5 pDDIs**	**6-10 pDDIs**	**≥ 11 pDDIs**	**P-value**
≥ 11	14	29	10	0.000
0-5 Drugs	1	0	0	
6-10 Drugs	27	12	3	

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