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PHARMACOVIGILANT ANALYSIS OF DRUG–DRUG INTERACTIONS ASSOCIATED WITH POLYPHARMACY IN CARDIAC PATIENTS AT GOVERNMENTAL HOSPITALS IN HYDERABAD, PAKISTAN

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ABSTRACT

Background/Objectives: Cardiovascular diseases (CVDs) remain as the leading cause of global morbidity and mortality and require long-term, multiple medication therapy. In Pakistan, the widespread use of multiple medications combined with the overall high prevalence of CVDs greatly increases the chances of drug-drug interactions (DDIs). This study was designed to evaluate the prevalence, patterns, severity, and clinical outcomes of DDIs among cardiac patients who used polypharmacy while being admitted to government hospitals in Hyderabad, Pakistan. It also sought to evaluate the relationship between polypharmacy and the number of DDIs present, and to discuss the relationship between the severity of the DDIs and patient survival using Kaplan-Meier analysis.

Methods: A retrospective cross-sectional observational design was used. Data was collected from 400 adult cardiac patients (≥18 years old) who were taking ≥ 5 medications. Sociodemographic, clinical and medication information was collected through a structured questionnaire. Drug-drug interactions were detected using standard interaction checkers and classified by type (PK/PD), severity (mild, moderate, severe), and clinical outcome. Statistical analysis was performed using IBM SPSS (version 28) using descriptive, and inferential methods including chi-square tests and Kaplan-Meier survival analysis.

Results: Out of 400 patients examined, polypharmacy was found to be common, averaging 9 medications per individual. At least one DDI was identified in 53% of prescriptions, with severe DDIs being most common (23% of total), followed by moderate (15%) and mild (15%). Most commonly found serious DDI combinations were: Anticoagulants and NSAIDS; Statins and Fibrates; Sacubitril/valsartan and ACE Inhibitors; Warfarin and Amiodarone. The clinical outcomes analyzed showed 25% dose reductions; 15% discontinuation; 60% no change to therapy. Kaplan-Meier studies [23] indicated that patients with severe DDIs had lower survival rates.

Conclusion: This study demonstrates the significant incidence of clinically relevant drug intervention (DDI) occurrences in cardiac patients with multiple medications treated in Pakistan. The presence of severe DDIs correlates with an increased risk of death; therefore, implementation of more comprehensive pharmacovigilance, use of DDI checking algorithms, and enhancement of clinical provider knowledge regarding the avoidance of DDIs, are necessary elements to assure patient safety and improvement of therapeutic outcomes.

KEYWORDS: Pharmacovigilance, Drug–Drug Interactions, Polypharmacy, Cardiac Patients, Pakistan, Survival Analysis

INTRODUCTION

The World Health Organization (WHO) describes 'Pharmacovigilance' as that scientific discipline whose priority is detecting, understanding, assessing and preventing any undesirable adverse effects associated with pharmaceutical products. Pharmacovigilance activities help improve the safe and effective use of medicines to promote safe use of medicines [1].

As a signatory to the WHO's International Drug Monitoring Programme, Pakistan's formal pharmacovigilance framework was not established until 2018. Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality in Pakistan, accounting for nearly 17.9 million deaths annually in 2021 [2]. As the CVDs experienced by patients require complex and long-term treatment with medications that frequently require

multiple medications at the same time (i.e. ≥ 5 per patient), polypharmacy tends to occur frequently among this patient population. While polypharmacy can assist in managing medical conditions, it also increases the potential for drug interactions, or 'DDI.' It has been well-documented that DDIs may result in serious and/or life-threatening ADRs, may negatively impact the therapeutic effectiveness of the combined medications prescribed, may result in hospitalization, and/or may result in death [3-6]. Despite the enormous clinical significance of DDI for all patients, pharmacotherapy literature pertaining to the prevalence, incidence, and consequences of DDI in CVD patients in this pais provides little data. [7-9].

Aims of this study are to evaluate the sociodemographic and clinical characteristics of patients with cardiac disease, to determine the prevalence, characteristics, severity and types of DDI's, to examine the relationship between levels of polypharmacy and the occurrence of DDI's, and to investigate the time to survive using Kaplan-Meier curves according to the severity of DDI's.

METHODOLOGY

Study Design

A retrospective cross-sectional observational design was used for data provided by patients at government hospitals in Hyderabad, Pakistan.

Study Setting

Governmental hospitals in Hyderabad, Pakistan.

Study Population

400 patients are included in the study who have received at least 5 medications by prescription and are 18 years of age or older.

Data Collection

Data regarding clinical history (comorbidities) and medication use was recorded using a structured questionnaire. Comorbidities that will be recorded are dyslipidemia, diabetes, obesity, smoking status, depression/anxiety, and benign prostatic hyperplasia (BPH) are to be recorded.

Classification

Identified DDIs were classified as either Pharmacokinetic or Pharmacodynamic, and severity will be classified as mild, moderate, or severe also clinical effect classifications.

Data Analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics version 28). A descriptive statistical analysis (frequency, percentage, median & interquartile range) will be performed. A normality check was performed using Kolmogorov-Smirnov and Shapiro-Wilk tests [10-12]. Inferential statistical tests included chi-square tests (to assess associations) with $p < 0.05$ being statistically significant. Polypharmacy groups will be established (5-7 medications; 8-10 medications; 11-12 medications) to compare patients who have one or more DDIs using chi-square tests and depicted in a line graph. Survival analyses were evaluated using Kaplan-Meier models and log rank will compare Kaplan-Meier curves based upon the groups identified by the severity of the DDI [26]. Mean survival time(s) was presented with a 95% confidence interval.

RESULTS

In a sample of 400 Cardiac Patients (CP), 100% of CP had Polypharmacy and the median number of medications CP had was 9 (5-12). The majority of CP in our study ranged from age 51-70 years old, and 55% male. The most prevalent comorbid conditions were Dyslipidemia (59%), Tobacco smoking (55%), Obesity (48%), Type 2 Diabetes Mellitus (31%), Depression/Anxiety (17%), and Ex-smoker (9%). The figure below displays the prevalence of the most frequently identified comorbid conditions in our CP sample.

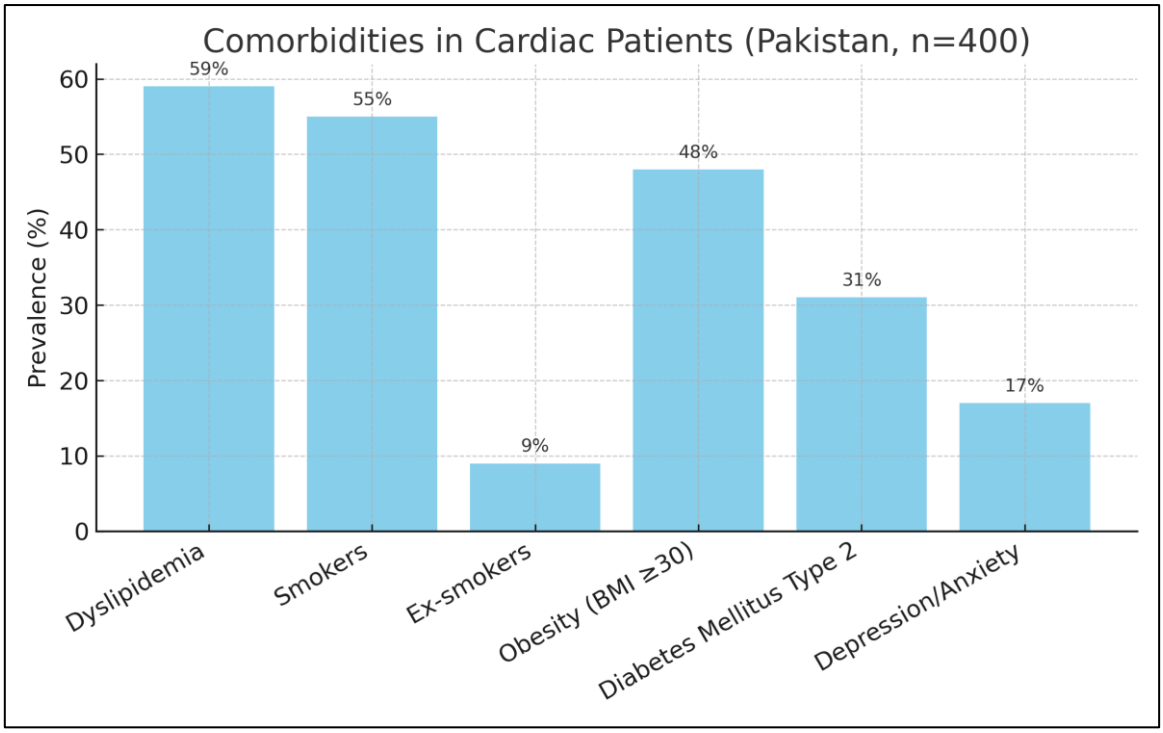

Figure 1. Prevalence of Comorbidities in Cardiac Patients in Hyderabad, Pakistan (n=400).

Dyslipidemia, Tobacco smokers, and Obesity were the three most prevalent comorbidities reported; Type 2 Diabetes, Depression/Anxiety and Ex-smokers were less common.

Prevalence: 53% of the total CP sample had At least One Drug-Drug Interaction (DDI) identified, of which 23% were Severe; 15% were Moderate; 15% were Mild.

Polypharmacy was significantly associated with the Presence of DDIs ($p < 0.001$). In particular, the number of medications prescribed had a significant Positive Association with Having at Least One DDI. Specifically, the % of CP in the Sample with at least one DDI was as follows: 37% of CP Taking 5-7 Medications; 59% of CP Taking 8-10 Medications; and 68% of CP Taking 11-12 Medications (Table 1).

Table 1. Relationship between the degree of Polypharmacy and the Presence of At least One DDI.

Polypharmacy group	Total # of prescription	No DDI	≥1 DDI	% of DDI
5-7 meds	137	86	51	37%
8-10 meds	160	66	94	59%
11-12 meds	103	33	70	68%
Total	400	185	215	54%

A Dose-Response Relationship is clearly illustrated such that as the Prescription Count Increases the Prevalence of DDIs also increases.

The information related to the relationship between the degree of polypharmacy (≥3 medications) and the increasing percentage of patients identified as being affected by drug-drug interactions (DDIs) of different levels of severity shown in Figure 2.

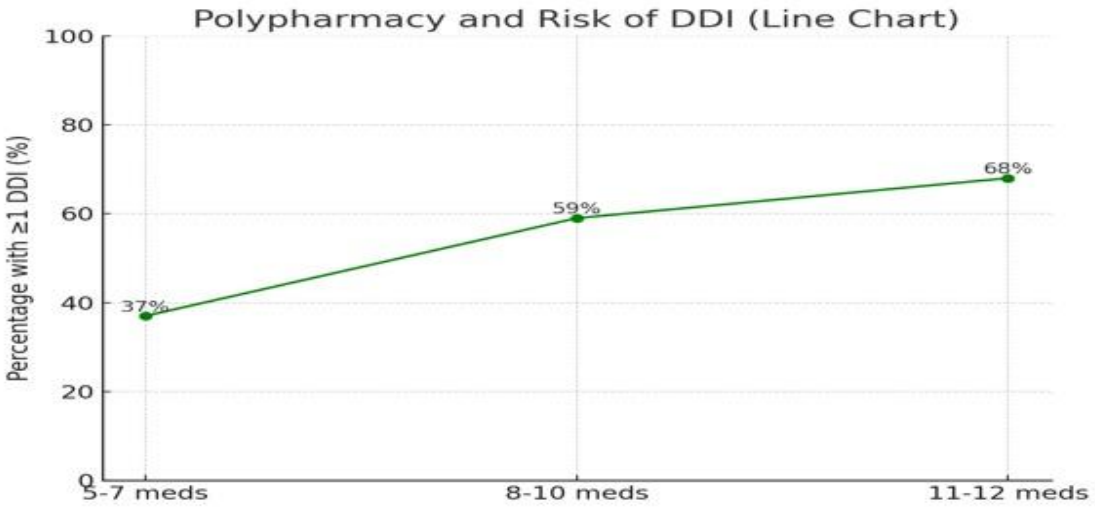

Figure 2. The Relationship Between Polypharmacy and Drug–Drug Interaction (DDI) Risk.

More specifically, when patients taking five, six, or seven medications were compared to those taking eight, nine, or ten, 37% of the former had at least one DDI, while 59% of the latter had at least one DDI. The final comparison of patients taking eleven or twelve medications to those taking eight through ten (68% had at least one DDI) illustrated a clear dose-response relationship between polypharmacy and DDIs.

Among DDI pairs, the most common combinations included anticoagulants plus NSAIDs, statins plus fibrates, sacubitril/valsartan plus ACE inhibitors, and warfarin plus amiodarone. In order to provide a comprehensive review of the number of occurrences of DDI pairs within the study population, further details concerning the occurrence of DDI pairs as well as their severity, mechanisms (pharmacokinetic or pharmacodynamic), and anticipated clinical impacts were presented in Figures 3 and 4 and Table 2. Table 1 and 2 contain a summary of the frequency with which various DDI pairs occurred, as well as the degree to which they were likely to result in high-risk combinations. For example, the combination of an anticoagulant and NSAID was noted as having the greatest potential risk to patients, as were the combinations of statins and fibrates.

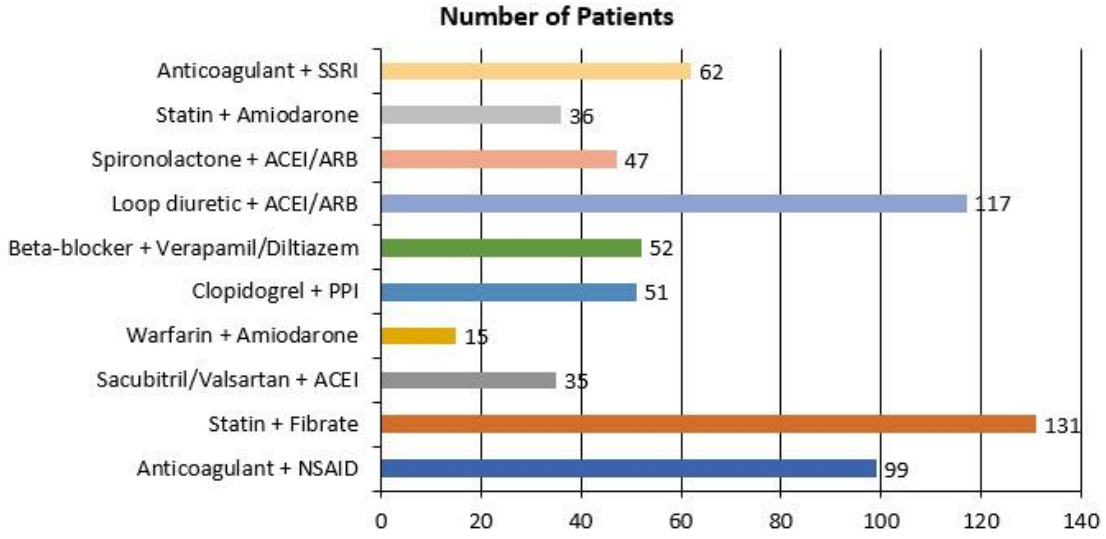

Figure 3. Most Common DDI Pairs observed in the study cohort.

Table 2. Characteristics of the most common DDI pairs, including severity, type, and clinical effect.

DDI Pair	No. of Patients	DDI Severity	DDI_Type	DDI Effect
Anticoagulant + NSAID	99	Severe	PD	↑ bleeding risk (GI, intracranial)
Statin + Fibrate	131	Severe	PK/PD	↑ risk of myopathy, rhabdomyolysis

Sacubitril/Valsartan + ACEI	35	Severe	PD	↑ risk of angioedema (contraindicated)
Warfarin + Amiodarone	15	Severe	PK	↑ INR, ↑ bleeding risk
Clopidogrel + PPI	51	Moderate	PK	↓ clopidogrel activation (reduced efficacy)
Beta-blocker + Verapamil/Diltiazem	52	Moderate	PD	↑ risk of bradycardia, AV block, hypotension
Loop diuretic + ACEI/ARB	117	Moderate	PD	↑ risk of hypotension, acute kidney injury
Spironolactone + ACEI/ARB	47	Moderate	PD	↑ potassium → hyperkalemia, arrhythmia
Statin + Amiodarone	36	Moderate	PK	↑ statin levels → muscle toxicity
Anticoagulant + SSRI	62	Moderate	PD	↑ bleeding tendency

Of those patients with DDIs, clinical interventions to resolve the interaction ranged from no clinical interventions (60%) to abrogation of the medication (15%) to adjustment of the medication dosage (25%).

Kaplan-Meier [26], survival analyses demonstrated that patients with severe DDIs had a shorter life expectancy than patients with moderate, mild, or no DDIs ($p<0.05$). This relationship is illustrated in Figure 4, which shows that as the severity of the DDI increases, the rate of decline in life expectancy accelerates; while the decline for moderate and mild DDIs also occurs, it occurs at a slower rate than severe DDIs.

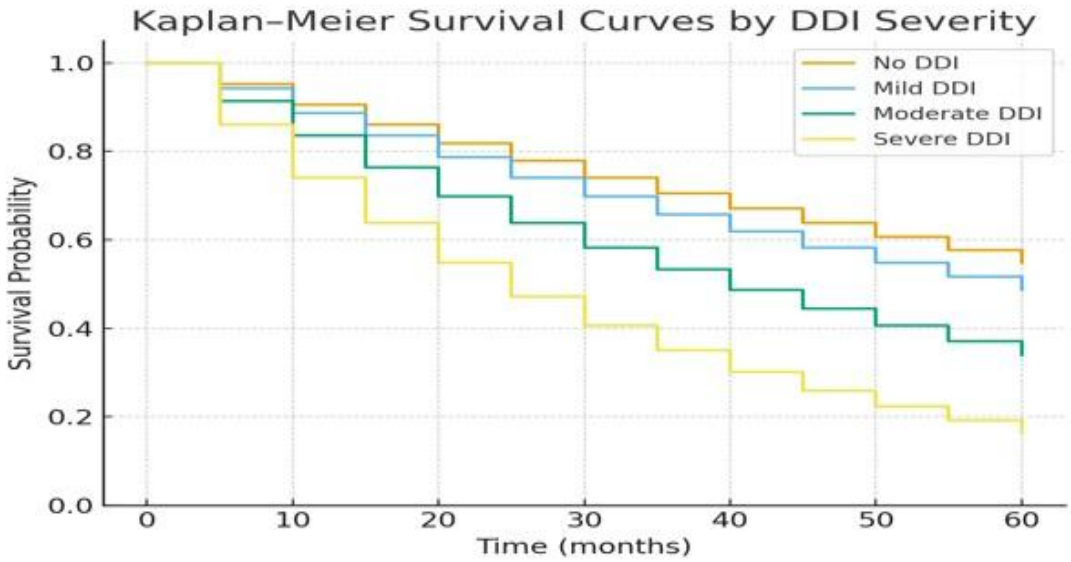

Figure 4. Kaplan–Meier survival curves by DDI severity.

Survival probability over follow-up is stratified by interaction severity (No DDI, Mild, Moderate, Severe). Life expectancy was negatively affected by the severity of drug-drug interactions, moderate are intermediate, and mild are close to no DDI.

DISCUSSION

A number of issues should be noted regarding this study that highlight the significant impact that drug-drug interactions (DDIs) have on the overall outcomes of cardiac patients taking multiple medications. The pattern of the relationship between polypharmacy level and DDI occurrence indicates that the value of medication review and the act of deprescribing has clinical utility in minimising the number of unnecessary combinations. The high prevalence of DDIs found in this sample group (53%) corresponds with international studies [13-17] that report

ranges from 30-60% depending on patient population and clinical setting. Moreover, the presence of severe DDIs is a concern, as 23% of those who took part in this study experienced at least one; therefore, it is critical that healthcare providers proactively monitor patients, particularly since those patients with severe or potentially severe DDIs have also been shown to have decreased life expectancy as a result of their DDI status in the Kaplan-Meier analysis [18-22]. Figure 4 illustrates the incremental disadvantage to survivorship that increased severity of DDI has placed on patients in this study, demonstrating the need for prompt recognition and response to DDIs in clinical practice. Frequent drug pairs identified in this study (i.e., anticoagulants and NSAIDs; statins and fibrates; and warfarin and amiodarone) have been reported in the literature as posing clinically significant DDIs [23-30]. The structured approach used in this study to identify and quantify the frequency of occurrence and clinical consequences of each of these DDI pairs can provide a basis for integrating pharmacovigilance systems into routine prescribing practice. Finally, the absence of action in relation to the majority (60%) of DDIs identified in this study signals a lack of adequate integration of pharmacovigilance systems within hospital clinical practice. The research highlights the necessity for integrating electronic DDI checking systems into hospital workflows, raising the awareness of healthcare professionals, and building strong pharmacovigilance systems nationwide. The study finds that Pakistan has the same challenges as LMICs in some ways; however, its pharmacovigilance system's novelty adds even more layers of complexity to these challenges.

CONCLUSION

The study found that every cardiac patient enrolled in the study was receiving at least one other drug (polypharmacy). More than half of these patients were experiencing at least one DDI, and many suffered from a severe DDI; however, the DDI-related mortality is clinically significant because the data indicates that mortality is much higher among patients who suffered from severe DDIs. Thus, this study indicates a need for reliable pharmacovigilance systems, the adoption of electronic DDI checking tools, and further education of all levels of healthcare providers to reduce DDI risk.

Recommendations

1. Implement routine use of electronic DDI checking systems in hospitals.
2. Provide ongoing education on pharmacovigilance and the management of patients receiving multiple medications.
3. Increase patient awareness of polypharmacy and adherence.
4. Create national guidelines for monitoring DDIs.
5. Conduct multicentre prospective research studies in order to increase the amount of evidence available regarding DDIs.

Limitations

1. Limited generalizability due to being a single-centre study.
2. Use of a cross-sectional design limits the ability to establish a causal relationship.
3. Data were obtained from a retrospective chart review.
4. Assessment of DDIs was reliant on external databases for the following: drug interactions (DI); drugs on the patient's current medication list.
5. The following potential confounding variables were unable to be controlled for (e.g., adherence or genetic variation).

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Institutional Review Board Statement
The Institutional Bioethics Committee of University of Sindh, Jamshoro, Pakistan, reviewed the research proposal and approved it ethically (ORIC/SU/143).

Informed Consent Statement
Informed written consent was obtained from each subject (parent or guardian if legally entitled), and all privacy of the subjects remained confidential.

Conflicts of Interest
The authors declare no conflict of interest

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