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Evaluation of Factors Contributing to Potential Drug-Drug Interactions in Cardiovascular Disease Management: A Retrospective Study

Awais Khan, Haya Hussain*

Department of Pharmacy, Shaheed Benazir Bhutto University Sheringal, 18000 Dir (Upper), Pakistan

* Correspondence: Haya Hussain (haya@sbbu.edu.pk)

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Abstract: A retrospective analysis was conducted to assess potential drug-drug interactions (pDDIs) in the management of cardiovascular diseases, evaluating 500 prescriptions from hospitalized patients between January 1 and April 1, 2023. Using Medscape online software for the identification of drug-drug interactions (DDIs) and SPSS version 21 for statistical analysis, the study documented a 93% occurrence rate of pDDIs across the prescriptions. These interactions were categorized as serious (15% of cases, n=760, maximum per encounter: 4, mean: 1.52 ± 1.064), significant (75.6% of cases, n=3855, maximum per encounter: 30, mean: 7.71 ± 4.583), and minor (9.5% of cases, n=485, maximum per encounter: 4, mean: 0.95 ± 1.025). On average, 9.5 medications were prescribed per patient. Factors significantly associated with the incidence of pDDIs included age ($r= 0.921$, $P < 0.01$), presence of concurrent diseases ($r= 0.782$, $P < 0.01$), length of hospital stay ($r= 0.559$, $P < 0.01$), and the number of prescribed drugs ($r= 0.472$, $P < 0.01$). The most frequent interacting combinations were identified, with Clopidogrel + Enoxaparin (38.15%, n=290) and Enoxaparin + Aspirin (26.92%, n=210) being the most common, followed by other notable combinations. The study recorded adverse drug reactions in 15 patients. This investigation highlights a significant prevalence of pDDIs, particularly in cases of polypharmacy among cardiovascular patients. It underscores the critical need for systematic analysis and vigilant monitoring of prescriptions prior to drug administration by healthcare professionals.

Keywords: Retrospective study; Tertiary care; Polypharmacy; Potential drug-drug interactions; Hospitalized patients

1. Introduction

When the effect of one drug is altered by the presence of another drug or this alteration occurs in the pharmacokinetics of a drug, such a phenomenon is called DDIs (Paloma & Isabel, 2010). DDIs may be pharmacokinetics or pharmacodynamics, which cause a decrease or increase in efficacy, increased toxicity of medications and treatment failure (Hansten & Horn, 2009; Baxter, 2010). Many drugs showed increased untoward effects or altered therapeutic responses due to DDIs (Baxter, 2010). In the case of indoor patients, DDIs need more attention because of their complex therapeutic regime, chronic disease, co-morbid conditions, severity of the diseases, frequent modifications in therapy and polypharmacy (Zwart-van Rijkom et al., 2009). Many recent studies have estimated the prevalence rate of pDDIs in hospital settings, which was found to be in the range of 27.8-51.4% (Cruciol-Souza & Thomson, 2006; Fokter et al., 2010). Taking an increased number of drugs, gender, old age, long hospital stays and co-morbid conditions have been reported as common risk factors for DDIs (Riechelmann et al., 2005; Johnell & Klarin, 2007; Nobili et al., 2009; Gagne et al., 2008; Doubova et al., 2007; Katona, 2001; Moura et al., 2009). DDIs can be prevented either by avoiding multiple drug therapies or by minimizing the potential benefits of drug combinations which are considered risk factors for the occurrence of clinically significant DDIs. It is reported that patients taking five drugs have about 40% pDDIs and those taking seven or more drugs have more than 80% pDDIs (Kapp et al., 2013; Grattagliano et al., 2010). These DDIs affect hospitalized patients more likely due to co-morbid conditions, multiple illnesses, frequent modifications in therapy,

chronic therapeutic regimens and polypharmacy (Zwart-van Rijkom et al., 2009). A study conducted in Switzerland in an internal medicine ward showed 56.2% of patients were exposed to one or more moderate or major pDDIs (Vonbach et al., 2008). It was reported in a study by Becker et al. (2007) that 0.054% of emergency department visits, 0.57% of hospital admissions and 0.12% of re-hospitalizations were caused by DDIs (Becker et al., 2007). In the Sub-Saharan region of Africa, a few studies have evaluated pDDIs (Lubinga & Uwiduhaye, 2011). It was reported in a study that about 33.5% of patients in Kenya receiving anti-retroviral therapy were exposed to clinically significant DDIs with their anti-retroviral drugs (Moura et al., 2009). This study aims to report the prevalence of pDDIs in prescriptions of hospitalized patients, their associations with risk factors like gender, age, and concurrent disease, the number of drugs per prescription, hospital stay and commonly occurring interacting drug combinations in the cardiology ward of a tertiary care hospital in Khyber Pakhtunkhwa, Pakistan.

2. Methodology

2.1. Study Design and Data Collection

This study is a cross-sectional retrospective study conducted at the cardiology ward of a tertiary care hospital using the prescriptions of hospitalized patients during a three-month period between January 1 and April 1, 2023. Prescriptions with incomplete records were excluded from this study.

2.1.1 Ethics approval

Ethical approval was granted for this study by the Ethical Committee of the Department of Pharmacy, Shaheed Benazir Bhutto University Sheringal Dir (Upper), Pakistan, with a notification number of SBBU/Pharm/22-129. To conduct this study in the cardiology ward, permission was obtained from the concerned ward in charge.

2.2 Data Analysis

The recorded data was analyzed using SPSS version 21. Medscape online software was used for the determination of DDIs. The data was presented as means and percentages.

3. Results

3.1 General Characteristics of Patients

This study sample comprises 500 hospitalized cardiovascular patients, with 250 (50%) male and 250 (50%) female. A total of 4,750 medications were recommended, including 2,359 (49.7%) and 2,391 (50.3%) for both sexes, respectively. It was found in this study that 93% (n=465) patients showed DDIs, including 48.4% (n=225) male and 51.6% (n=240) female patients, and 7% (n=500) patients showed no DDIs. The age of the patients recorded in this study ranges from 21 to 100 years, with a median age of 55 years. The length of their stay at the hospital ranges from one to eleven days, with a median of six days. The number of medications prescribed per prescription ranges from three to 20 drugs, with a median of 9.5 drugs, as shown in Table 1.

Table 1. General characteristics of patients

Variables	Number of Patients and the Proportions (%)	Number of Patients with DDIs and the Proportions (%)	Number of Patients with No DDIs and the Proportions (%)	Number of Drugs Prescribed and the Proportions (%)
Gender				
Male	50 (50)	225 (48.4)	25 (71.4)	2,359 (49.7)
Female	50 (50)	240 (51.6)	10 (28.6)	2,391 (50.3)
Total	100	465 (100)	35 (100)	4,750
Age (years)				
≤ 1	0 (0)			
1-20	0 (0)			
21-40	45 (9)			
41-60	280 (56)			
61-80	155 (31)			
81-100	20 (4)			
≥100	0 (0)			
Median	50 years			
Range	1-100 years			
Hospital stays (days)				

< 2	40 (8)
2-4	370 (74)
5-7	60 (12)
8-10	15 (3)
>10	15 (3)
Median	6 days
Range	1-11 days
Number of drugs prescribed per prescription (n=4750)	
< 3	0 (0)
3-6	120 (24)
7-10	255 (51)
11-14	75 (15)
15-18	40 (8)
>18	10 (2)
Median	9.5 drugs
Range	3-20 drugs

3.2 Types of DDIs

A total of 5,100 DDIs (maximum per encounter: 33) with a mean of 10.16 ± 5.422 were observed and categorized as serious (14.9% of cases, n=760, maximum per encounter: 4, mean: 1.52 ± 1.064), significant (75.6% of cases, n=3855, maximum per encounter: 30, mean: 7.71 ± 4.583) and minor (9.5% of cases, n=485, maximum per encounter: 4, mean: 0.95 ± 1.025) types of DDIs, as shown in Table 2.

Table 2. Types of DDIs

Types of DDIs	Max DDIs	Sum of DDIs (%)	Mean ± SD
Serious DDIs	4	760 (14.9)	1.52 ± 1.064
Significant	30	3855 (75.6)	7.71 ± 4.583
Minor DDIs	4	485 (9.5)	0.95 ± 1.025
Total DDIs	33	5100 (100)	10.16 ± 5.422

3.3 Frequencies for All Types of DDIs

Out of 500 prescriptions, 35 (7%) were found to have no DDIs, with only 5 (1%) having one DDI. The remaining 360 (72%) prescriptions were identified as having multiple DDIs. Specifically, the distributions of DDIs were as follows: 5 prescriptions each contained 2 and 4 DDIs; 20 prescriptions had 5 DDIs; 40 contained 6 DDIs; 10 had 7 DDIs; 65 contained 8 DDIs; 50 had 9 DDIs; and 70 prescriptions were identified with 10 DDIs. In the higher range of interactions, 25 prescriptions contained 11 DDIs, 30 had 12, another 25 contained 13, 10 had 14, 40 contained 15, 20 had 16, 15 contained 17, 5 had 19, and another 10 prescriptions were identified with 20 DDIs. At the extreme, 5 prescriptions each were found to have 22, 24, and 33 DDIs. These distributions are illustrated in Figure 1.

3.4 Frequencies of Serious DDIs

Among 500 prescriptions, 100 were found to have no serious DDIs, with 140 having only one serious DDI. The remaining 180, 60, and 20 prescriptions were found to have 2, 3, and 4 serious DDIs, respectively, as shown in Figure 2.

3.5 Frequencies of Significant DDIs

Only 35 prescriptions were identified with no significant DDIs, with the remaining 5 having a single significant DDI. Out of these 360 prescriptions, 5, 20, 20, 50, 90, 45, 50, 45 and 25 prescriptions were identified with 2, 3, 4, 5, 6, 7, 8, 9 and 10 significant DDIs, respectively, while the remaining 30, 20, 25, 10, 5, 5 and 5 were identified with 11, 12, 13, 14, 15, 16 and 18 significant DDIs, respectively, as shown in Figure 3.

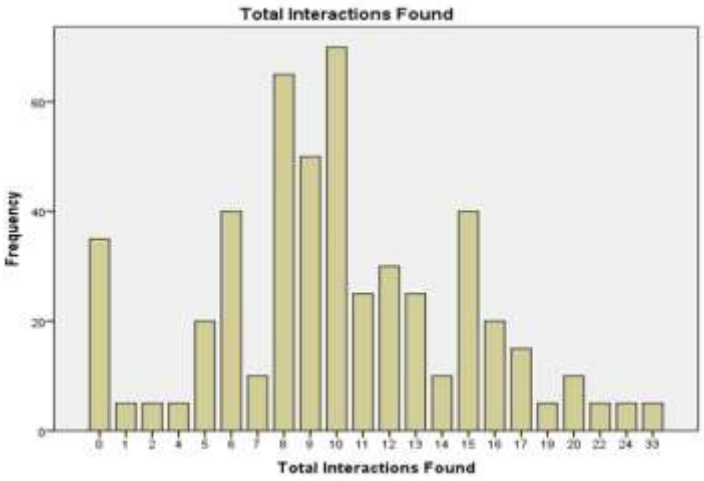

Figure 1. Frequencies for all types of DDIs

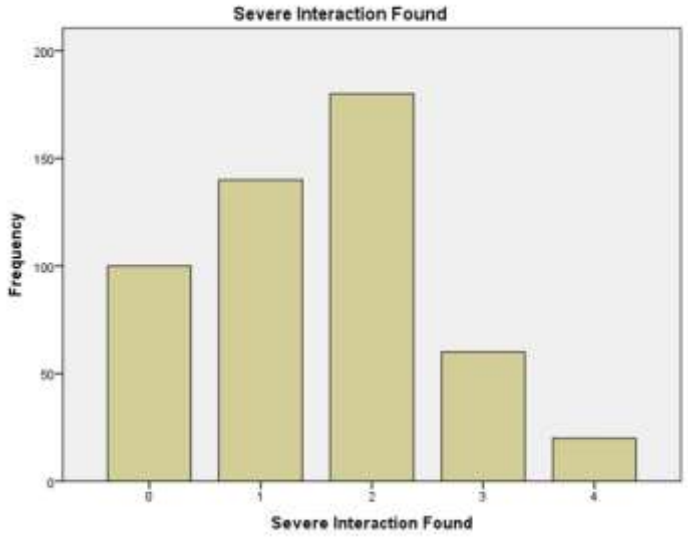

Figure 2. Descriptive statistics for serious DDIs

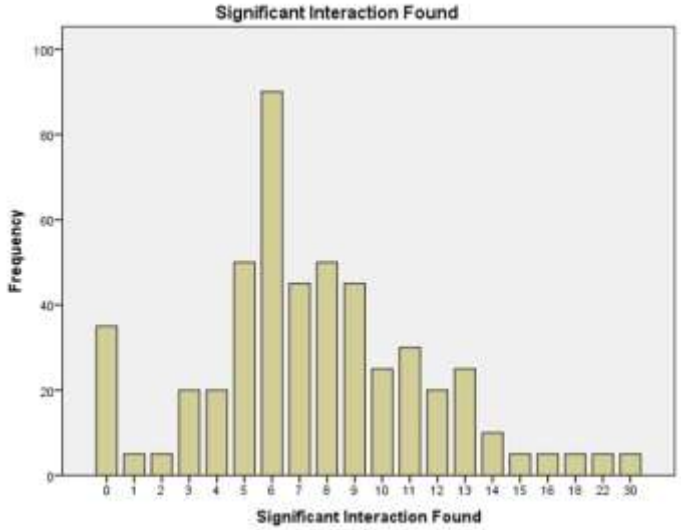

Figure 3. Frequency of significant DDIs

3.6 Frequencies of Minor DDIs

Out of 500 prescriptions, 195 were found to have no minor DDIs. However, the remaining 185, 75, 30 and 15 were identified with 1, 2, 3 and 4 minor DDIs, respectively (Figure 4).

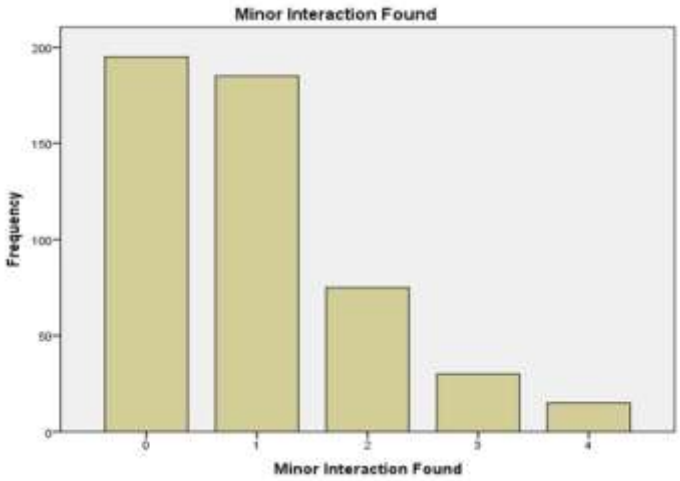

Figure 4. Frequency of minor DDIs

3.7 pDDIs in Relation to Various Risk Factors

3.7.1 pDDIs in relation to age

In the analysis of 500 patient prescriptions, it was determined that DDIs varied significantly across different age groups. Among the age groups studied, 45 patients aged 21-40 years were identified, presenting with 480 DDIs (mean: 10.67 ± 4.743). This cohort displayed 75 serious DDIs (mean: 1.67 ± 0.674), 370 significant DDIs (mean: 8.22 ± 4.011), and 35 minor DDIs (mean: 0.78 ± 0.636). In the 41-60 years age bracket, 280 patients were identified with a total of 2845 DDIs (mean: 10.16 ± 6.108), including 400 serious DDIs (mean: 1.43 ± 1.180), 2175 significant DDIs (mean: 7.77 ± 5.188), and 275 minor DDIs (mean: 0.98 ± 1.062). Among the 155 patients aged 61-80 years, 1625 DDIs were recorded (mean: 10.48 ± 4.139), consisting of 265 serious DDIs (mean: 1.71 ± 0.890), 1210 significant DDIs (mean: 7.81 ± 3.535), and 165 minor DDIs (mean: 1.06 ± 1.049). Lastly, the smallest group, comprising 20 patients aged 81-100 years, was associated with 130 DDIs (mean: 6.50 ± 4.199), including 20 serious DDIs (mean: 1.00 ± 1.026), 100 significant DDIs (mean: 5.00 ± 3.078), and 10 minor DDIs (mean: 0.50 ± 0.889). A positive correlation was observed between age and the incidence of DDIs across all categories: serious (r = 0.658**), significant (r = 0.949**), minor (r = 0.331**), and total DDIs (r = 1**), with all correlations being statistically significant (P < 0.01), as depicted in Table 3.

Table 3. pDDIs in relation to age

Age (years)		Serious DDIs	Significant DDIs	Minor DDIs	Total DDIs
21-40 (N=45)	Sum	75	370	35
	Mean ± SD	1.67 ± .674	8.22 ± 4.011	0.78 ± .636
41-60 (N=280)	Sum	400	2175	275
	Mean ± SD	1.43 ± 1.180	7.77 ± 5.188	0.98 ± 1.062
61-80 (N=155)	Sum	265	1210	165
	Mean ± SD	1.71 ± 0.890	7.81 ± 3.535	1.06 ± 1.049
81-100 (N=20)	Sum	20	100	10
	Mean ± SD	1.00 ± 1.026	5.00 ± 3.078	0.50 ± .889
Total (N=500)	Sum	760	3855	485
	Mean ± SD	1.52 ± 1.064	7.71 ± 4.583	0.97 ± 1.025
	r	0.658**	0.949**	0.331**

SD: Standard deviation; r: Pearson correlation coefficient; **: Correlation is significant at the 0.01 level (i.e., P < 0.01, bivariate, Pearson, 2-tiled correlation between age and DDIs found).

3.7.2 pDDIs in relation to concurrent diseases

It was found in this study that 60 prescriptions associated with patients having no concurrent diseases exhibited 360 DDIs (mean: 6.00 ± 4.510), which included 30 serious DDIs (mean: 0.50 ± 0.873), 315 significant DDIs (mean:

5.25 ± 3.798), and 15 minor DDIs (mean: 0.25 ± 0.437). For patients with 1-2 concurrent diseases (n=135 prescriptions), 1345 DDIs were documented (mean: 9.96 ± 5.048), comprising 225 serious DDIs (mean: 1.67 ± 1.191), 1000 significant DDIs (mean: 7.71 ± 3.904), and 125 minor DDIs (mean: 0.93 ± 1.188). Patients with 2-3 concurrent diseases (n=220 prescriptions) were associated with 2335 DDIs (mean: 10.61 ± 5.304), including 355 serious DDIs (mean: 1.61 ± 0.860), 1745 significant DDIs (mean: 7.93 ± 4.775), and 250 minor DDIs (mean: 1.14 ± 0.970). In the group with 4-5 concurrent diseases (n=65 prescriptions), 775 DDIs were identified (mean: 11.92 ± 5.023), consisting of 110 serious DDIs (mean: 1.69 ± 0.999), 605 significant DDIs (mean: 9.31 ± 4.880), and 60 minor DDIs (mean: 0.92 ± 0.735). Finally, for patients with more than five concurrent diseases (n=20 prescriptions), 265 DDIs were found (mean: 13.25 ± 6.463), including 40 serious DDIs (mean: 2.00 ± 1.257), 190 significant DDIs (mean: 9.50 ± 4.894), and 35 minor DDIs (mean: 1.75 ± 0.330). A positive correlation was observed between the number of concurrent diseases and all categories of DDIs: serious (r = 0.658**), significant (r = 0.949**), minor (r = 0.331**), and total DDIs (r = 1**), all statistically significant (P < 0.01), as demonstrated in Table 4.

Table 4. pDDIs in relation to concurrent diseases

Number of Concurrent Diseases		Serious DDIs	Significant DDIs	Minor DDIs	Total DDIs
0 (N=60)	Sum	30	315	15	360
	Mean ± SD	0.50±0.873	5.25±3.798	0.25±0.437	6.00±4.510
1-2 (N=135)	Sum	225	1000	125	1345
	Mean ± SD	1.67±1.191	7.71±3.904	0.93±1.188	9.96±5.048
2-3 (N=220)	Sum	355	1745	250	2335
	Mean ± SD	1.61±0.860	7.93±4.775	1.114±0.970	10.61±5.304
4-5 (N=65)	Sum	110	605	60	775
	Mean ± SD	1.69±0.999	9.31±4.880	0.92±0.735	11.92±5.023
>5 (N=20)	Sum	40	190	35	265
	Mean ± SD	2.00±1.275	9.50±4.894	1.75±1.333	13.25±6.463
Total (N=500)	Sum	760	3855	485	5080
	Mean ± SD	1.52±1.064	7.71±4.583	0.97±1.025	10.16±5.422
	r	0.658**	0.949**	0.331**	1

SD: Standard deviation; r: Pearson correlation coefficient; **: Correlation is significant at the 0.01 level (i.e., P < 0.01, bivariate, Pearson, 2-tiled correlation between the age and DDIs found).

3.7.3 pDDIs in relation to hospital stay

During the study, hospital stay durations were closely monitored, ranging from less than two days to more than ten days. Analysis was performed on the correlation between the length of hospital stay and the incidence of DDIs. It was found that 40 patients who stayed for less than two days experienced 165 DDIs, with a mean of 4.13 ± 4.485, including 10 serious DDIs (mean: 0.25 ± 0.439), 150 significant DDIs (mean: 3.75 ± 4.229), and 10 minor DDIs (mean: 0.25 ± 0.439). For the 370 patients staying between two to four days, 3705 DDIs were documented (mean: 10.01 ± 5.107), comprising 535 serious DDIs (mean: 1.45 ± 0.933), 2840 significant DDIs (mean: 7.68 ± 4.488), and 345 minor DDIs (mean: 0.93 ± 0.950). Patients staying five to seven days (n=60) were associated with 800 DDIs (mean: 13.33 ± 5.115), which included 135 serious DDIs (mean: 2.25 ± 1.019), 585 significant DDIs (mean: 9.75 ± 4.605), and 80 minor DDIs (mean: 1.33 ± 1.188). Those who stayed for seven to nine days (n=15) had 170 DDIs (mean: 11.33 ± 2.717), including 30 serious DDIs (mean: 2.00 ± 0.845), 115 significant DDIs (mean: 7.67 ± 1.291), and 25 minor DDIs (mean: 1.67 ± 1.759). Furthermore, 15 patients who stayed for more than ten days encountered 240 DDIs (mean: 16.00 ± 0.845), consisting of 50 serious DDIs (mean: 3.33 ± 0.976), 165 significant DDIs (mean: 11.00 ± 1.690), and 25 minor DDIs (mean: 1.67 ± 1.759). Statistical analysis revealed a positive correlation between the length of hospital stay and the total number of DDIs, categorized into serious, significant, and minor interactions. The Pearson correlation coefficients were significant (serious DDIs: r = 0.658**, significant DDIs: r = 0.949**, minor DDIs: r = 0.331**, and total DDIs: r = 1; P < 0.01), as presented in Table 5.

3.7.4 pDDIs in relation to drugs prescribed per prescription

The patient cohort was categorized based on the range of prescribed drugs: 120 patients were prescribed 3-6 drugs, 255 received 7-10 drugs, 75 were prescribed 11-14 drugs, 40 received 15-18 drugs, and 10 were prescribed more than 18 drugs. Patients prescribed 3-6 drugs experienced 615 DDIs (mean: 5.13 ± 4.051), including 55 serious DDIs (mean: 0.46 ± 0.647), 525 significant DDIs (mean: 4.38 ± 3.548), and 55 minor DDIs (mean: 0.46 ± 0.869). Those prescribed 7-10 drugs encountered 2560 DDIs (mean: 10.04 ± 4.476), with 385 categorized as serious (mean: 1.51 ± 0.726), 1955 as significant (mean: 7.67 ± 4.318), and 220 as minor (mean: 0.86 ± 0.688). Patients prescribed 11-14 drugs had 1050 DDIs (mean: 14.00 ± 2.847), including 170 serious (mean: 2.27 ± 0.859), 780 significant (mean: 10.40 ± 3.179), and 100 minors (mean: 1.33 ± 1.201). Those prescribed 15-18 drugs reported 635 DDIs

(mean: 15.88 ± 1.786), with 125 serious (mean: 3.13 ± 0.607), 425 significant (mean: 10.63 ± 2.084), and 85 minor (mean: 2.13 ± 1.285). Patients prescribed more than 18 drugs experienced 220 DDIs (mean: 22.00 ± 2.108), consisting of 25 serious (mean: 2.50 ± 1.581), 170 significant (mean: 17.00 ± 5.270), and 25 minor (mean: 2.50 ± 1.581). A positive correlation was observed between the number of drugs per prescription and the total DDIs, which was statistically significant across all categories: serious (r = 0.658**), significant (r = 0.949**), minor (r = 0.331**), and total DDIs (r = 1; P < 0.01), as shown in Table 6.

Table 5. pDDIs in relation to hospital stay

Length of Stay (Days)		Serious DDIs	Significant DDIs	Minor DDIs	Total DDIs
< 2 (n=40)	Sum	10	150	10	165
	Mean ± SD	0.25±0.439	3.75±4.229	0.25±0.439	4.13±4.485
2-4 (n=370)	Sum	535	2840	345	3705
	Mean ± SD	1.45±0.933	7.68±4.488	0.93±0.950	10.01±5.107
5-7 (n=60)	Sum	135	585	80	800
	Mean ± SD	2.25±1.019	9.75±4.665	1.33±1.188	13.33±5.115
8-9 (n=15)	Sum	30	115	25	170
	Mean ± SD	2.00±0.845	7.67±1.291	1.67±1.759	11.33±2.717
> 10 (n=15)	Sum	50	165	25	240
	Mean ± SD	3.33±0.976	11.00±1.690	1.67±1.759	16.00±0.845
Total (N=500)	Sum	760	3855	485	5080
	Mean ± SD	1.52±1.064	7.71±4.583	0.97±1.025	10.16±5.422
	r	0.658**	0.949**	0.331**	1

SD: Standard deviation; r: Pearson correlation coefficient; **: Correlation is significant at the 0.01 level (i.e., P < 0.01, bivariate, Pearson, 2-tiled correlation between the age and DDIs found); and N = ∑n.

Table 6. pDDIs in relation to drugs prescribed per prescription

Number of Drugs Per Prescription		Serious DDIs	Significant DDIs	Minor DDIs	Total DDIs
3-6 (N=120)	Sum	55	525	55	615
	Mean ± SD	0.46±0.647	4.38±3.548	0.46±0.869	5.13±4.051
7-10 (N=255)	Sum	385	1955	220	2560
	Mean ± SD	1.51±0.726	7.67±4.34	0.86±0.688	10.04±4.476
11-14 (N=75)	Sum	170	780	100	1050
	Mean ± SD	2.27±0.859	10.40±3.179	1.33±1.201	14.00±2.847
15-18 (N=40)	Sum	125	425	85	635
	Mean ± SD	3.13±0.607	10.63±2.084	2.13±1.285	15.88±1.786
>18 (N=10)	Sum	25	170	25	220
	Mean ± SD	2.50±1.581	17.00±0.5.270	2.50±1.581	22.0±2.108
Total (N=500)	Sum	760	3855	485	5080
	Mean ± SD	1.52±1.064	7.71±0.4.583	0.97±1.025	10.16±5.422
	r	0.658**	0.949**	0.331**	1

SD: Standard deviation; r: Pearson correlation coefficient; **: Correlation is significant at the 0.01 level (i.e., P < 0.01, bivariate, Pearson, 2-tiled correlation between the age and DDIs found).

Table 7. Characteristics of the most frequent serious pDDI combinations

Type of Combinations	Number of Combinations and the Proportions (%)	Effects	Management
Clopidogrel+Enoxaparin	290 (38.1)	↑ Risk of bleeding	Close monitoring
Enoxaparin+Aspirin	210 (27.6)	↑ Unusual bleeding	Close monitoring
Ramipril+Spironolactone	70 (9.2)	↑ Risk of hyperkalemia	Close monitoring
Furosemide+Ceftriaxone	25 (3.2)	Cause arrhythmia	Close monitoring
Esomeprazole+Clopidogrel	20 (2.6)	↓ Effectiveness of clopidogrel	Dose adjustment
Enoxaparin+Ceftriaxone	20 (2.6)	↑ Effect of enoxaparin	Use with caution
Valsartan+Spironolactone	20 (2.6)	↑ Risk of hyperkalemia	Close monitoring
Digoxin+Carvedilol	9 (1.1)	Cause bradycardia	Use with caution
Enoxaparin+Warfarin	5 (0.6)	↑ Risk of bleeding	Close monitoring
Furosemide+Insulin	5 (0.6)	Cause hyperglycemia	Blood sugar monitoring

3.8 Most Frequent Drug Combinations for Serious DDIs and Their Effects

The analysis revealed the ten most frequently occurring serious pDDIs in the study cohort. The combination of Clopidogrel and Enoxaparin was identified as the most prevalent, occurring 290 times and accounting for 38.15% of serious interactions. This was followed by Enoxaparin and Aspirin, recorded 210 times (26.92%). Other notable drug combinations included Ramipril and Spironolactone, which appeared 70 times (9.21%); Furosemide and Ceftriaxone, 25 times (3.28%); and Esomeprazole with Clopidogrel, Enoxaparin with Ceftriaxone, and Valsartan with Spironolactone, each recorded 20 times (2.63%). Further, Digoxin combined with Carvedilol appeared 9 times (1.1%), and the combinations of Enoxaparin with Warfarin and Furosemide with Insulin were each noted 5 times (0.6%). These findings are detailed in Table 7.

4. Discussion

This study reveals that 93% pDDIs are prevalent in a total of 500 patient medications prescribed, which is higher than 91.6% reported by Murtaza et al. (2016), and 77.7% reported by Ismail et al. (2012) in Ayub Teaching Hospital. Comparative studies have demonstrated variable prevalence rates of pDDIs in cardiac patients. Research conducted at a south Indian hospital reported a prevalence of 30.67% (Patel et al., 2011), while another study in an Iranian hospital documented a higher prevalence of 43.4% (Namazi & Moosavi, 2012). These variations underscore the complexity and multiplicity of treatment regimens often necessary in cardiac care, which frequently involve a high number of cardiac drugs (Albadr et al., 2014).

In this study, serious pDDIs were observed in 15% of cases (n=760, maximum per encounter: 4) with a mean of 1.52 ± 1.064, a figure considerably lower than the 45% reported by Ismail et al. (2012) in ATH, Pakistan. Conversely, significant pDDIs were recorded in 75.6% of prescriptions (n=3855, maximum per encounter: 30) with a mean of 7.71 ± 4.583, substantially exceeding the rates previously noted by Ismail et al. (2012). Additionally, minor pDDIs were identified in 9.5% of cases (n=485, maximum per encounter: 4) with a mean of 0.95 ± 1.025.

The number of drugs prescribed per prescription is 9.5, which is higher than the values reported in earlier studies: 4.5 in Pakistan (Das et al., 2001), 3.9 in Nigeria (Erah et al., 2003), 3.5 in Iran (Cheraghali et al., 2004) and 1.3 in Zimbabwe (Hogerzeil et al., 1993).

This study shows that some factors are concerned with pDDIs, including age, concurrent disease, long hospital stay and polypharmacy. Various factors significantly associated with pDDIs in different studies have also been found. This study shows that there are no relationships between gender and pDDIs. In addition, old age is a risk factor for pDDIs ($P < 0.01$) and is positively correlated with serious, significant, minor and total pDDIs ($r = 0.658$, 0.949, 0.331 and 1, respectively). There is a significant positive linear relationship between the age of patients and pDDIs ($r= 0.921$, $P < 0.01$). This observation is consistent with other studies (Mallet et al., 2007; Bacic-Vrca et al., 2010). A study conducted in Switzerland in cardiovascular patients also revealed that patients with old age were at greater risk for pDDIs (Egger et al., 2007). Another study of cardiovascular patients also indicates that pDDIs increase significantly with age (Carter et al., 2002). The predominant cause of these interactions in older populations has been attributed to the higher number of prescribed medications, necessitated by comorbidities such as hypertension, diabetes, and ischemic heart diseases (Chelkeba et al., 2013). In this study, comorbidities including hypertension, ischemic heart diseases, diabetes, chronic obstructive pulmonary diseases, and hepatitis were observed to significantly elevate the risk of pDDIs ($P < 0.01$). Positive correlations were found between the presence of concurrent diseases and the incidence of serious, significant, and minor pDDIs, as well as the total number of pDDIs ($r = 0.658$, 0.949, 0.331, and 1, respectively). Similarly, there is a positive linear relationship between the number of concurrent diseases and pDDIs ($r= 0.782$, $P < 0.01$). Doubova et al. (2007) proposed that the increased number of prescribed drugs enhanced the pDDIs. The most common drug pairs involved in these interactions are cardiovascular drugs, consistent with findings from earlier studies (Köhler et al., 2000).

This study shows that long hospital stay ($P < 0.01$) is one of the factors associated with the occurrence of pDDIs. The length of hospital stay is positively correlated with serious, significant, minor, and total pDDIs ($r = 0.658$, 0.949, 0.331 and 1, respectively). There is a positive linear relationship between the length of hospital stay and pDDIs ($r= 0.559$, $P < 0.01$). A study conducted for cardiovascular patients shows that long hospital stay is associated with the occurrence of pDDIs (Patel et al., 2014). According to a study conducted in Brazil, pDDIs are significantly associated with longer hospital stay (Riechelmann et al., 2005). Some other studies also support the relationship between longer hospital stay and pDDIs proposed in this study (Moura et al., 2009).

This study shows that patients taking multiple drugs have a higher risk of pDDIs ($P < 0.01$). In addition, serious, significant, minor and total pDDIs are positively correlated with the number of drugs per prescription ($r = 0.658$, 0.949, 0.331 and 1, respectively). There is a positive linear relationship between the number of prescribed drugs and pDDIs ($r= 0.472$, $P < 0.01$). A study conducted in India shows that patients taking multiple-drug therapies are at a higher risk of pDDIs (Patel et al., 2014). Egger et al. (2007) proposed that the rate of pDDIs for cardiac patients in Switzerland increased with the increase in the number of drugs prescribed. A similar association was observed in a study conducted in the USA for hypertensive patients (Carter et al., 2004).

The top ten most frequent pDDI combinations found in this study are the concomitant use of Clopidogrel with Enoxaparin, which occurred 290 times (38.15%), followed by the concomitant use of Enoxaparin with Aspirin, which occurred 210 times (26.92%), and Enoxaparin with Warfarin, which occurred five times (0.6%). Pharmacologically, these pairs have serious interactions in terms of bleeding enhancement risk, which is an additive effect. These findings align with those of earlier studies, which stated that the concomitant use of Aspirin, Clopidogrel and Enoxaparin is associated with gastrointestinal bleeding (Ng et al., 2008). Another study indicates that the concomitant and longer use of Clopidogrel and anticoagulants increases the risk of gastrointestinal bleeding (Lanas et al., 2011). Ramipril with Spironolactone combination occurred 70 times (9.21%) in this study, which pharmacologically can cause a serious risk of hyperkalemia. Research carried out by Cravedi et al. (2010) showed that the concomitant use of Spironolactone with an ACE inhibitor carried a significant risk of hyperkalemia (Cravedi et al., 2010). The concomitant use of Digoxin with Carvedilol occurred nine times (1.1%), which pharmacologically may cause bradycardia. An earlier study showed that this type of combination appears to cause bradycardia in cardiac patients (Khand et al., 2003). Valsartan + Spironolactone combination occurred 20 times (2.6%), which can pharmacologically cause hyperkalemia. A study conducted by Leone et al. (2000) shows that the concomitant use of Valsartan with Spironolactone looks like a safe approach for elderly hypertensive patients with chronic heart failure but not acute myocardial infarction (MI). This study shows that Enoxaparin + Ceftriaxone combination occurred 20 times (2.63%), which can pharmacologically enhance the effect of Enoxaparin. A study conducted by Juárez-Cedillo et al. (2016) indicates that the concomitant use of Enoxaparin with Ceftriaxone increases the risk of bleeding due to the increased effect of Enoxaparin. This study shows that Esomeprazole + Clopidogrel combination occurred 20 times (2.63%). A study conducted by Kenngott et al. (2010) shows that the concomitant use of proton pump inhibitors (PPIs) with Clopidogrel may interact with cytochrome p450 isozyme 2C19 (CYP2C19), leading to the decreased effectiveness of Clopidogrel. This study shows that Furosemide + Ceftriaxone combination occurred 25 times (3.28%), which can pharmacologically cause arrhythmia because Ceftriaxone reduces the diuretic potential of Furosemide due to some unknown mechanism (Korn et al., 1986). In addition, this study shows that Furosemide + Insulin combination occurred five times (0.6%). Furosemide decreased Insulin released by inhibiting Cl^- and Ca^{2+} fluxes in beta cells when both drugs were concomitantly used (Sandstrom & Sehlin, 1988).

4.1 Limitations of This Study

This retrospective study evaluated the occurrence of DDIs across 500 prescriptions at a single hospital, highlighting that the findings might not be generalizable to other hospitals. Therefore, a pilot study is recommended throughout the country for further exploration of pDDIs. The pDDIs in this study may be used as a precaution to use alternative medications and closely monitor the treatment regimens and patient outcomes.

5. Conclusion

It can be concluded in this study that most of the prescriptions indicate a high prevalence rate of pDDIs for cardiovascular patients. In addition, a higher number of drugs prescribed per prescription may lead to polypharmacy. To mitigate the risks associated with pDDIs, a pharmacist-physician review team is recommended for properly analyzing and carefully monitoring prescriptions prior to drug administration.

Data Availability

The data used to support the research findings are available from the corresponding author upon request.

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Conflicts of Interest

The authors declare no conflict of interest.

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