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Potential drug-drug interactions in Hospitalized Cardiac Patients in Asir region.

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List of abbreviations:

CCU	Cardiac care unit.
DDI	Drug-Drug interaction.
pDDI	potential drug-drug interaction.
CVDs	cardiovascular diseases.

Abstract:

Background: Drug-drug interactions (DDIs) are a major cause for concern in patients with cardiovascular disorders due to multiple co-existing conditions and the wide class of drugs they receive.

Objectives: The objective of our study was to identify potential drug-drug interactions among hospitalized cardiac patients and to identify the risk factors associated with these interactions.

Methods: After obtaining approval from Institutional Ethical Committee, a prospective observational study was carried out among 200 hospitalized cardiac patients in aseer hospital. Cardiac patients prescribed at least two drugs and having hospital stay of more than 24-hour duration were enrolled into the study. The prescriptions were analyzed for potential DDIs using Micromedex multidrug interaction checker tool. Descriptive statistics, Student 't' test, ANOVA and Pearson correlation coefficient were used to analyze the results.

Results: The incidence of potential DDIs was 93% moderate interactions, 91.5% major interactions and 30.5 % minor interactions with 200 prescriptions having at least one potential DDI. 110 potentially interacting drug pairs were identified among which major and moderate interactions were of significant grade while only seven were minor interactions. Aspirin/clopidogrel (111), furosemide /aspirin (89), enoxaparin and clopidogrel (89) and Lisinopril / aspirin (60) were the most common interacting pairs. Drugs most commonly involved were aspirin, clopidogrel, heparin, furosemide, ranitidine and Lisinopril. The risk factors found associated with the potential DDIs Were Age, polypharmacy, and diabetes mellitus.

Conclusions: Proper therapeutic planning, routine monitoring of cardiac inpatients and usage of online DDI database will avoid potentially hazardous consequences in cardiac in-patients.

Keywords: DDIs, Micromedex, Cardiac in-patients.

1.1. Introduction:

The incidence of cardiovascular diseases (CVDs) has increased in recent decades. It has been estimated that CVDs are responsible for 46% of death in Saudi Arabia.

Drugs are usually used to produce beneficial therapeutic effect but, they can also lead to undesirable effects such as increased, reduced or null therapeutic effect (**1).** These can be due do interactions between the drugs administrated together **(2).**

Cardiovascular disease patients are exposed to drug -drug interactions (DDIs) due to large number of drugs they are receiving, most of them are elderly and the heart disease may change the drug metabolism. The type of the interaction also varies according to the nature of the disease, the individual and the other drugs being used **(3).**

Drug –Drug interaction is very important issues to discuss in patients receiving multi drug therapy as this interaction may lead to increased risk of hospitalization and health cost **(4)**

When the effect of one drug is altered by the administration of another drug it is called DDI **(5).**

There are two types of the DDI; pharmacokinetics and pharmacodynamics interactions. The pharmacokinetic interaction occurs when either of the concurrently administered drugs have potential to alter other's pattern of absorption, distribution, metabolism and excretion. While, pharmacodynamics interaction occurs if concurrently administered drugs have similar or opposite effects **(6).**

In primary healthcare, 9.2% to 78.8% of patients are reported to be at risk of a potential drug-drug interaction (pDDI) due to concomitant administration of drugs **(7).**

1.2. Literature review

The incidence of cardiovascular diseases has significantly increased in the recent decades. They are regarded as a leading cause of deaths worldwide **(8).**

Furthermore, patients with cardiovascular disorders are even at higher risk of DDI due to large number of drug they are receiving and the influence of heart disease on drug metabolism **(9).**

The drug therapy has grown more complex with the increasing load of patients with multiple disease states. The complex therapeutic regimens increase the risk of drug-drug interaction (DDI) to a great extent **(10).**

DDI is occur when the drug is taken together with the second drug and change in a drugs effect on the body **(11).**

The large a number of severe adverse drug reactions (ADR) resulting in emergency department visits and hospitalizations. It is estimated that DDI contribute to about 6-30% of all ADRs **(12)**.

Also, every year DDI accounts for about 2.8% of hospital admission **(13).**

The potential of the cardiovascular drug in the development of DDI is relatively higher as shown in the studies conducted worldwide.

In one of the teaching hospitals in India, A prospective study conducted indicated that the incidence of potential drug interaction amongst cardiac drugs in hospitalized patients is 30.67% **(14)**.

A study in Palestine among patients receiving antihypertensive medications came up with 433 different unique pairs of potential drug interactions among 867 patients **(15).**

Another study from Nepal regarding DDI indicated that 53% of the patients admitted to the Department of Internal Medicine experience one or more DDIs **(16).**

Also, another study in Nepal to evaluate the pattern of DDI amongst diabetic outpatients also found that 47.5% of medications potentially interacting with antidiabetics were cardiovascular drugs **(17).**

Some studies have found that DDIs are responsible for up to 2.8 % of patient's admission to hospital and 11% of patients experience symptoms associated with DDIs **(18, 19).**

However, in other studies that have been done in pediatrics, they find that the incidence of actual occurrence of DDIs has been reported to be much smaller, ranging from 0 to 1.3% **(20, 21).**

According to a recently published study, 1% of all hospital admissions are caused by DDIs, and 0.05% emergency department visits, 0.6% of the hospital admissions and 0.1% of re‑hospitalizations are caused by adverse drug reactions (ADRs) due to DDIs **(22,23).**

The study conducted by **Jankel CA.,** also shown that DDIs are associated with increased health care use (**24).**

In the study conducted **by Ghulam Murtaza et al**., the most common diagnosis was myocardial infarction followed by acute coronary syndrome and coronary artery disease. Upon analysis, they found 5109 of pDDIs. The prevalence of pDDIs in this study was 91.6% **(25).**

There is a study performed in the Cardiology ward of University Clinical Hospital Center in Serbia, which has been done on 527 patients, with more than one prescription during hospital stay. They found that at least 83.9% of patients have drug-drug interactions especially in patients with higher number of drugs **(26).**

Our aim is to identify the prevalence of drug –drug interactions (DDI) among hospitalized cardiac patients. Furthermore, we will assess the severity of risk of this interaction.

2.1. Aim of the study:

The study aims to identify the prevalence of drug –drug interactions (DDI) among hospitalized cardiac patients.

2.2. Study objective:

- Assess the severity of risk of this interaction.
- Assess the correlation between number of drugs prescribed, comorbidities and the incidence of DDIs.

3.1. Materials and methods:

3.2. Study design, population and data collection

A prospective observational study were carried out for a period of 3 months (February –April 2018) in a tertiary care hospital. Ethical approval were obtained from Institutional ethics committee prior to initiation of the stud**y.**

3.3. Study type

Prospective observational

3.4. Study area

Saudi Arabia, Asir Region

3.5. Sample size:

200 prescriptions were analyzed during the study period**.**

Certain demographic characteristics were studied to find out the predictors of DDIs, such as patient characteristics [gender, age (more than 18 years old) and concurrent morbidities], drug characteristic (number of drugs).

3.6. Inclusion Criteria:

- Patients who were admitted consecutively to cardiology unit
- All patients aged 18 years or older admitted to the hospital and had a length of stay greater than 24 hours.

3.7. Exclusion Criteria:

- Patients referred to the cardiology unit for evaluation,
- Patients visiting on outpatient basis and patients who died during hospital stay.

3.8. Classification and analysis of the drug – drug interactions

Each patient's electronic medication list and medication orders in the chart were evaluated. Micromedex interaction databases were used to provide an objective and consistent assessment of the presence and clinical significance of potential drug-drug interactions.[18,19] When a potential drug-drug interaction were identified by the Micromedex databases, the interacting drugs, doses, routes of administration and the database severity rating were recorded. The patient's sex and age will be also recorded.

3.9. Data Analysis

After a potential drug-drug interaction were identified, a severity assessment was conducted with the Micromedex databases. The mean age and sex of the patients in the

study were determined. Descriptive statistics were performed on the collected data to enable the development of a list of the most frequently occurring and clinically significant potential drug-drug interactions.

Results were expressed as percentage for age, gender, diagnosis, number of drugs prescribed, severity and risk involved. Chi-square test were done to study the association of number of drugs prescribed, comorbidities, age and sex with pDDI.

Table 1: severity Risk:

Major	Effects may result in death, hospitalization, permanent injury, or therapeutic failure
Moderate	Medical intervention needed to treat effects; effects do not meet criteria for major
Minor	Effects would be considered tolerable in most cases; no need for medical intervention

4.1. Results:

Table 2: Demographic characteristics (Gender)

	Frequency	Percent	Chi-Square	p-value
Male	120	60.0	8.000	0.005
Female	80	40.0		

Figure 1:

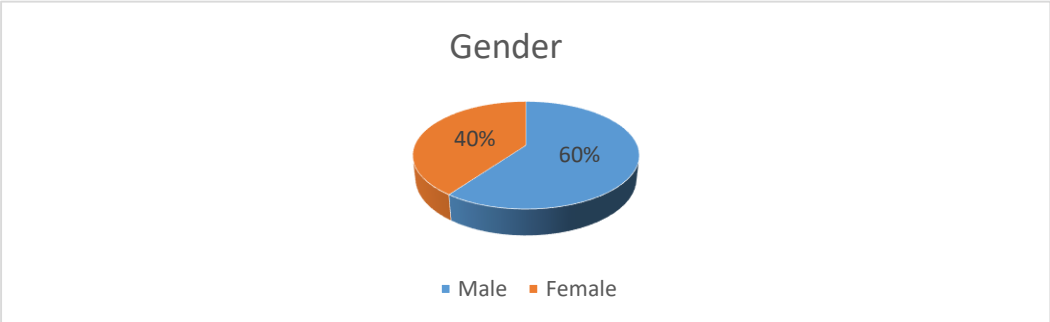


Table 3: Age

A.G

Cumulative Percent	Valid Percent	Percent	Frequency		
5.0	5.0	5.0	10	30-40	Valid
29.0	24.0	24.0	48	51-60	
50.0	21.0	21.0	42	61-70	
81.5	31.5	31.5	63	more than 70	
100.0	18.5	18.5	37	41-50	
	100.0	100.0	200	Total	

Test Statistics

	A.G
Chi-Square	37.650[a]
Df	4
Asymp. Sig.	.000

a. 0 cells (0.0%) have expected frequencies less than 5. The minimum expected cell frequency is 40.0.

Figure 2:

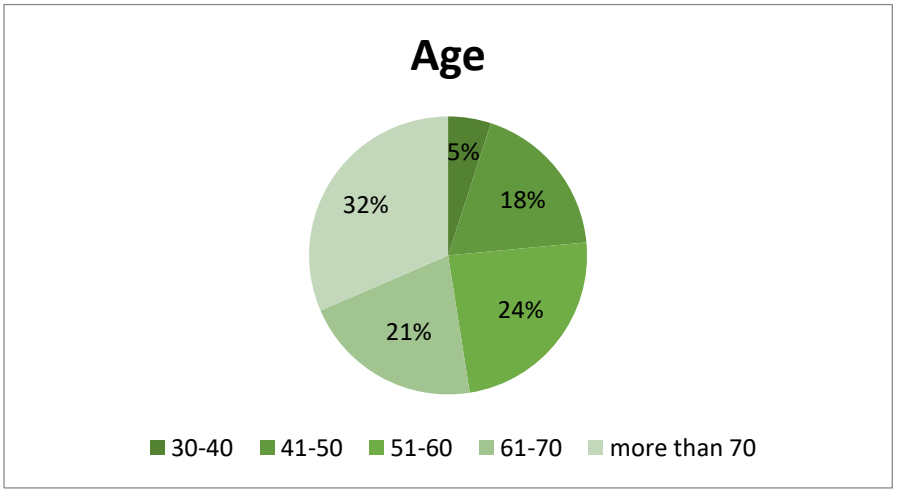


Table 4: the Number of drugs prescribed

		Frequency	Percent	Chi-Square	p-value
Number of drugs	1-3	1	.5	168.080	0.000
	4-6	15	7.5		
	7-9	67	33.5		
	more than10	117	58.5		

Figure 3 : Number of drugs prescribed for the patients

This figure showed that the Number of drugs prescribed to the cardiac patients when the most patients take more than 10 drugs were 59% then 9-7 drugs in 33% and 6-4 drugs 8%.

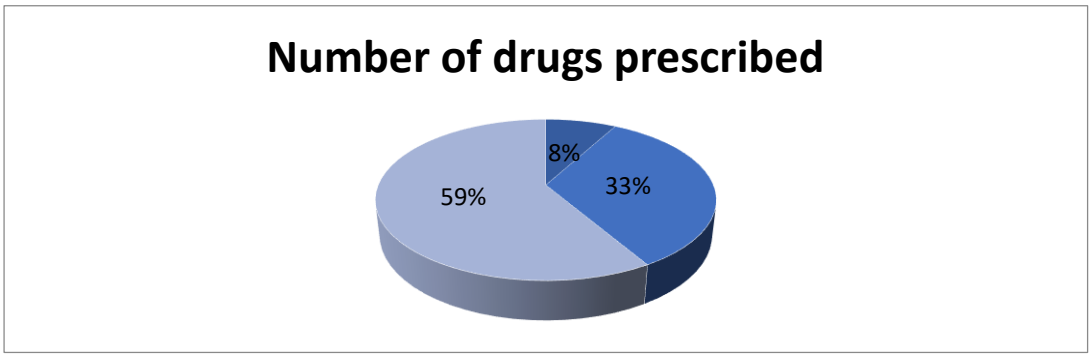


Table 5: severity of the pDDIs:

		Frequency	Percent	Chi-Square	p-value
Major interaction	Yes	183	91.5	137.780	0.000
	No	17	8.5		
Moderate interaction	Yes	186	93.0	147.920	0.000
	No	14	7.0		
Minor interaction	Yes	61	30.5	30.420	0.000
	No	139	69.5		

Figure 4: severity of the pDDIs

This figure showed that the severity of DDI in 200 patients. Moderate DDI it is the most common 93% then Major DDI is present in 91.50% times and 30.50% is the number of the frequent minor DDI in the patients. (Figure 4)

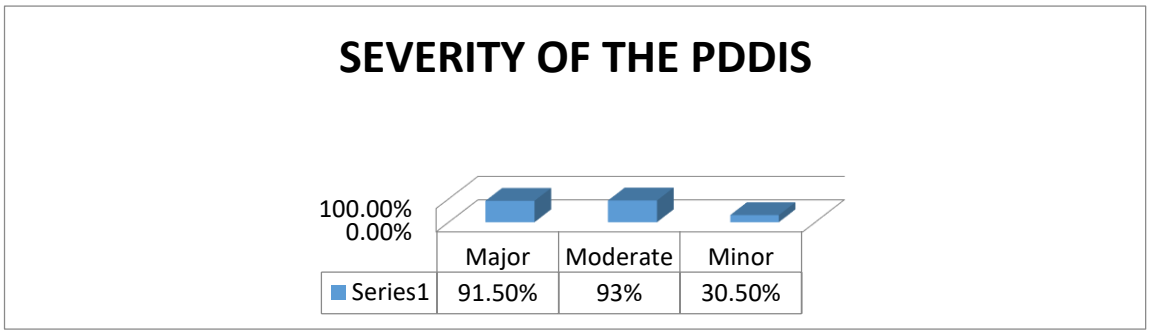


Table 6: The most commonly prescribed drugs.

		Frequency	Percent	Chi-Square	p-value
Anticoagulants and antiplatelet	yes	195	97.5	183.322	0.000
	no	4	2.0		
Diuretics	yes	112	56.0	2.880	0.090
	no	88	44.0		
Antihypertensive	yes	123	61.5	10.580	0.001
	no	77	38.5		
Calcium channel blocker	yes	30	15.0	97.090	0.000
	no	169	84.5		
ACE inhibitors	yes	113	56.5	3.663	0.056
	no	86	43.0		
Adrenergic inhibitors	yes	116	58.0	5.472	0.019
	no	83	41.5		
Vasodilators	yes	57	28.5	36.307	0.000
	no	142	71.0		
ARB	yes	17	8.5	135.838	0.000
	no	181	90.5		
Inotropic agents	yes	16	8.0	140.146	0.000
	no	183	91.5		

Figure 5: The most commonly prescribed drugs

This figure showed that most commonly prescribed drugs Anticoagulants and Antiplatelet, Antihypertensive (97.50%, 62%) respectively. (Figure 5)

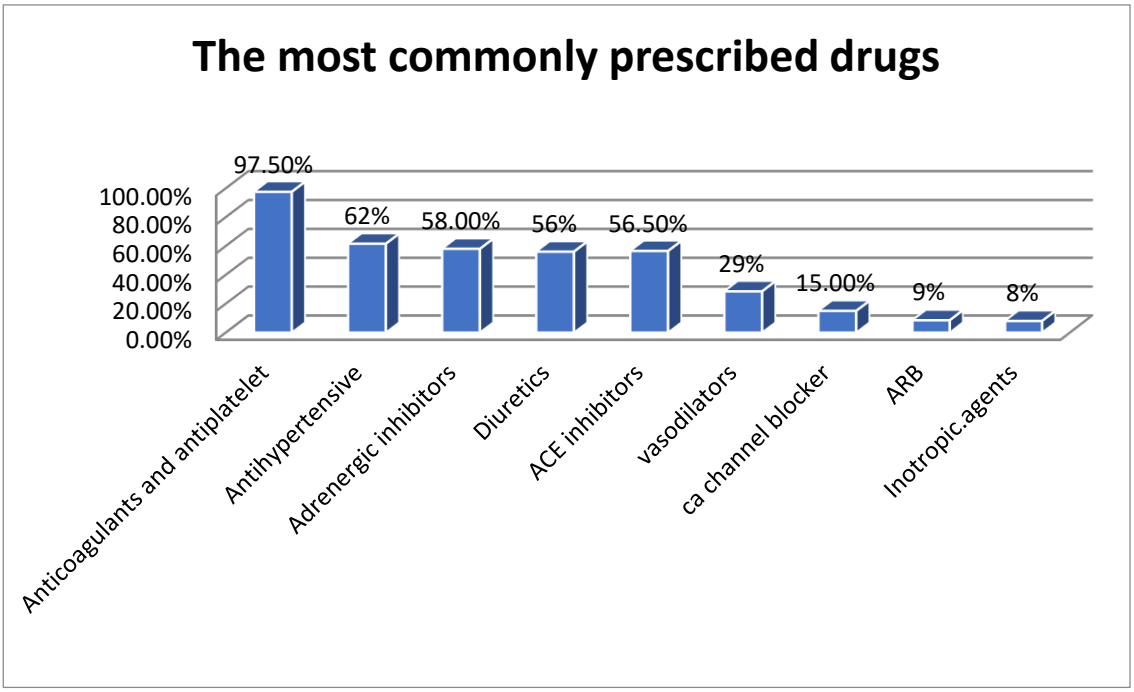


Table 7: most common diagnosis diseases

		Frequency	Percent	Chi-Square	p-value
Hypertension	yes	145	72.5	40.5	0.000
	no	55	27.5		
Coronary artery disease	yes	97	48.5	0.180	0.671
	no	103	51.5		
Atrial fibrillation	yes	18	9.0	134.480	0.000
	no	182	91.0		
Congestive heart failure	yes	58	29.0	35.280	0.000
	no	142	71.0		
Cardiomyopathy	yes	11	5.5	158.420	0.000
	no	189	94.5		
	yes	2	1.0	192.080	0.000

Valvular heart disease	no	198	99.0		
Rheumatic heart disease	yes	0	0	38.720	0.000
	no	200	100.0		

This table shows the most common diagnosis diseases in the patients. Rheumatic heart disease100 % , Valvular heart disease 99% ,Cardiomyopathy 94%.

Figure 6: The Diagnosis

This figure showed that the most common cardiac diseases in the patients. Hypertension 41% then Coronary artery disease 27%. Finally, Congestive heart failure and Myocardial infarction came in 16%. (Figure 6)

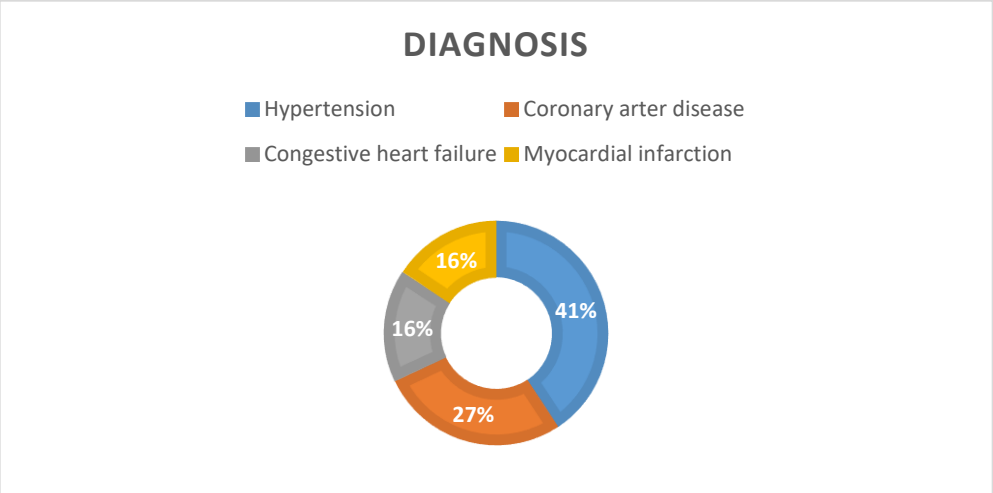


Table 8: The most common comorbidities in patients with pDDIs

		Frequency	Percent	Chi-Square	p-value
Diabetes	yes	121	60.5	8.820	0.003
	no	79	39.5		
CKD		15	7.5	405.075	0.000
Lung disease		9	4.5		
BPH		2	1.0		
Hypothyroidism		2	1.0		
G.I.T		3	1.5		

Figure 7: The most common comorbidities in patients with pDDIs

This figure showed that the most common comorbidities in patients with pDDIs is DM, CKD, Lung Disease (84% 10%, 6%) respectively. (Figure 7)

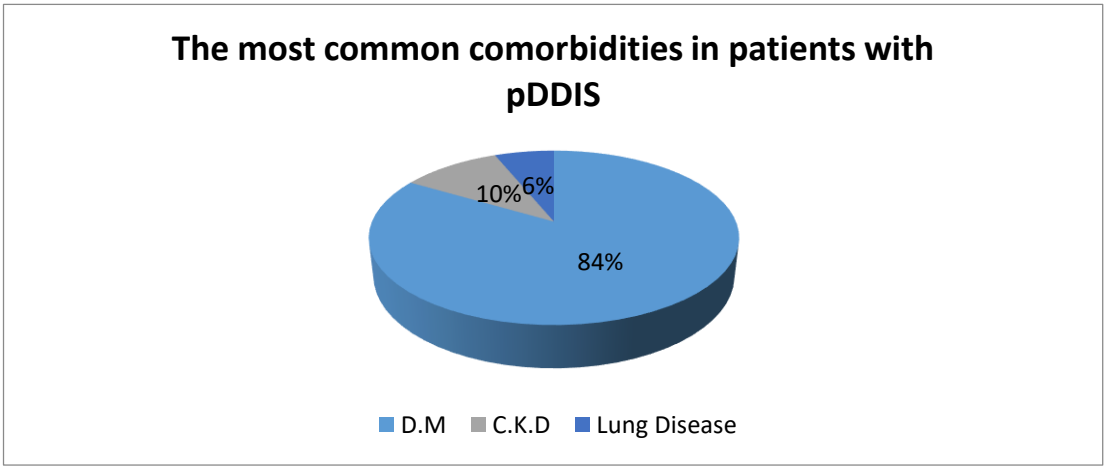


Table 9:

Top 10 major interaction

Interact	Frequency	Percent
clopidogrel and aspirin	111	18.5
furosamide and aspirin	89	10.5
enoxaparin and clopidogrel	89	10.5
Heparin and aspirin	52	7
clopidogrel and omeprazole	47	5.5
spironolactone and aspirin	29	11.5
clopidogrel and esomeprazole	22	2.6
enoxaparin and Heparin	20	2.4
ticagrelor and aspirin	18	2.1
clopidogrel and Heparin	16	3.6

Table 10:

Top 10 moderate interaction

Interact	Frequency	Percent
lisinopril and aspirin	60	9.3
metoprolol and aspirin	58	10.8
insulin and aspirin	49	10.3
carvedilol and aspirin	40	5.3
lisinopril and furosamide	32	5.0
insulin and lisinopril	27	4.2
enalapril and aspirin	26	6.7
bisoprolol and aspirin	24	5.6
levofloxacin and aspirin	16	7
clopidogrel and atrovastatin	12	1.9

Table 11:

Top 10 Minor interaction

Interact	Frequency	Percent
rantidine and aspirin	41	58.5
furosamide and hydralazine	24	34.3
dobutamine and metoprolol	2	2.8
gentamicin and amoxicillin	1	1.4
gentamicin and ampicillin	1	1.4
warfarin and levothyroxine	1	1.4

Figure 8: Relationship between number of Drugs prescribed and the pDDIs.

This figure showed that the number of drugs that used by the patients increase the risk of DDIs increased . (Figure 8)

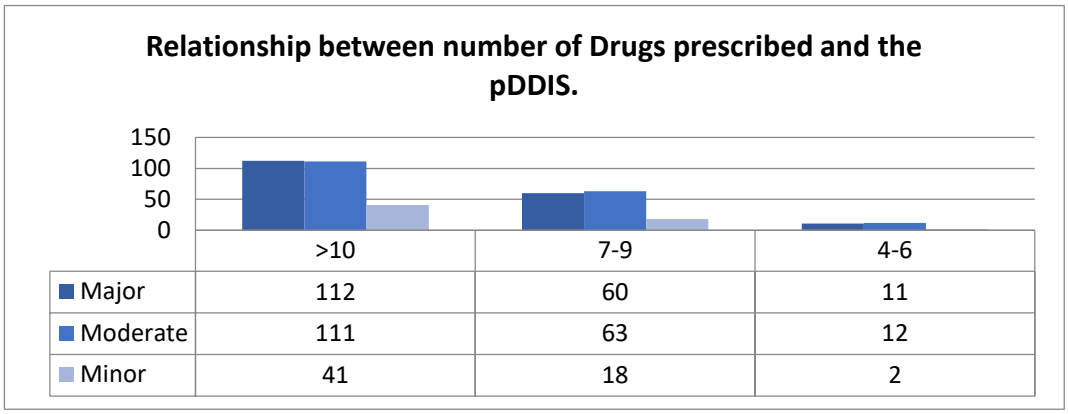


Figure 9: Relationship between the age and potential Major DDIs

This figure showed that Relationship between the age and potential Major DDIs with 58% of Major DDIs in patients more than 70 years and 6% in patients between 30 and 40 years old. (Figure 9)

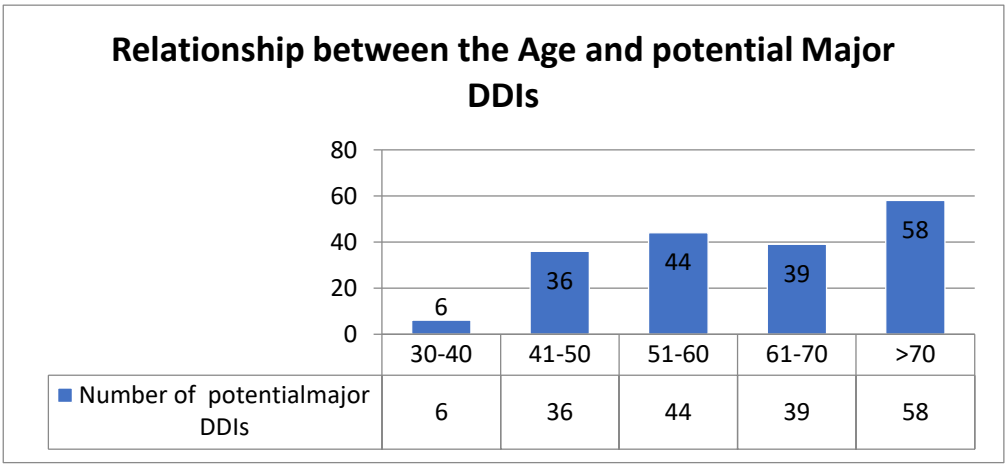
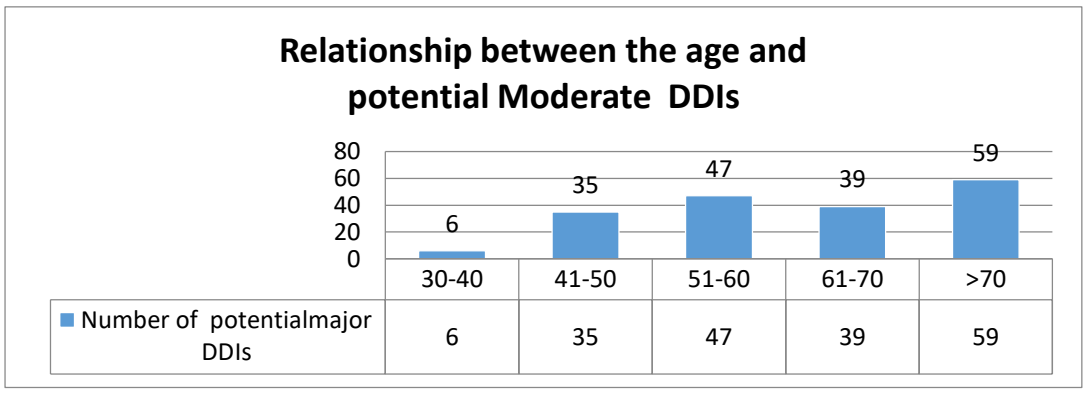


Figure 10 : Relationship between the age and potential Moderate DDIs

This figure showed that 59% of Moderate DDIs in patients more than 70 years and 6% in patients between 30 and 40 years old. (Figure 10)



5.1.Discussion:

Cardiovascular disease patients are exposed to drug -drug interactions (DDIs) due to the large number of drugs they are receiving, DDIs occur when the effect of one drug is altered by the Co administration of another drug. Cardiovascular diseases (CVD) have a significant share in the disease burden on societies worldwide.

They are attributed a high morbidity and mortality rate, and significant economic burden derived from medical costs and working incapacity. however, increasing rate of multimorbidity and drug use leads to therapy becoming more complex and challenging, There are two types of the DDI; pharmacokinetics and pharmacodynamics interactions, the pharmacokinetic interaction occurs when either of the concurrently administered drugs have potential to alter other's pattern of absorption, distribution, metabolism and excretion. While, pharmacodynamics interaction occurs if concurrently administered drugs have similar or opposite effects.

Among the 200 prescriptions analyzed, the majority (58%) were in the age group of >70 years, which similar to the study of Ansha Subramanian et al **(27).** (44%) 51-60 years. the incidence rate of pDDIs showed an increasing trend with the age and this could be because the mean number of drugs per prescription was higher in the elderly patients with coexisting co-morbidities. A study done by Kashyap et al **(28)** shows similar findings.

One of our findings that no correlation between gender and drug -drug interactions . this findings is consistent with the results of a study done by Murtaza et al **.(29)** but differ from a study done by Shanbhag et al .which showed a higher incidence of DDI in females compared to males **(30)** .The most common diagnosis with cardiac diseases was Hypertension 41%, then Coronary artery disease 27%. Finally Congestive heart failure and Myocardial infarction came in 16%.

The most common drugs prescribed in our study were Anticoagulants and antiplatelet (195 [97.5%]), Antihypertensive (123 [61.5%]), Adrenergic inhibitors (116 [58%]).On analyzing the severity of the interactions, majority of the identified pDDIs were of significant grade (91%), moderate (93%) and minority (30.5%). The top major interacting pairs were Clopidogrel and Aspirin 111 (18.5%) and that mean the most interactions were between an antiplatelet groups of drugs these findings are similar to study done by Patel et al.32 and Smithburger et al.33 but differ from observations done

by Sharma et al.34 where atorvastatin and enalapril were the most common drugs involved in DDIs

These findings are similar to studies done by AjayD et al **(31).**

The top moderate interaction Lisinopril and aspirin (60 [9.3%]). And the top minor interactions Rantidine and Aspirin (41 [58.5%]). Relation between number of drugs and majority of drug-drug interactions. We found that the increase of the number of drugs increases DDI and majority. More than 10 drugs major interactions were 117. And the positive linear relationship was also found between diabetes mellitus and pDDIs. As many, previous studies showed the same results such as AjayD et al **(31).**

The number of drugs prescribed to the cardiac patients when the most patients take more than 10 drugs, 59%, then 9-7 drugs in 33% and 6-4 drugs, 8%, because the patients diagnosed with disease such as hypertension, diabetes mellitus, chronic kidney disease,etc. In our study the most common comorbidities in patients with bodice is DM in 84%, then CKD in 10% and Lung Disease 6%.

The most common comorbidity 121 diabetes patients with major and moderate interactions because the Patients have many multiple medications are started. In addition, many diabetes educators are confused by drug interaction terminology and rely heavily on pharmacists and prescribers. Followed by 15 patients chronic kidney disease because Individuals with chronic kidney disease (CKD) often require multiple classes of drugs being at important risk for the development of DDIs.

Monitoring and continuous follow up over longer durations are required to identify of DDI.

6.1. Conclusion:

The high incidence of potential DDIs among cardiac inpatients in our study highlights the need to respond appropriately to keep a check on some of the potentially hazardous consequences.

Age, number of medicines prescribed and presence of diabetes mellitus were the risk factors identified in this study.

6.2. Recommendation:

- One of the ways to minimize the consequences of DDIs would be to use the DDI database freely available online, by both clinicians.

- We recommend to activate the role of clinical pharmacist in the hospitals for close monitoring of the files.

7.1. data collection form:

Table 1: Diagnosis of patients with cardiovascular diseases in a tertiary care hospital

Diagnosis
Hypertension
Coronary heart disease.
Atrial fibrillation
Congestive heart failure
Cardiomyopathy
Valvular Heart disease.
Rheumatic Hear disease.
Others.

Table 2: Types of drugs that will be prescribed to the cardiovascular patients.

Drugs
Anticoagulants and antiplatelet.
Diuretics.
Antihypertensive.
Calcium channel blockers.
ACE inhibitors.

Adrenergic inhibitors.
Vasodilators.
ARB.
Inotropic agents.
Others

Table 3: severity Risk:

The interacting pairs	Severity risk
1	Major
2	Moderate
3	Minor

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