A Retrospective Observational Cohort Study on Drug-Drug Interactions among the Hospitalized Patients in the Cardiology Department of a Tertiary Care Hospital

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ABSTRACT
Studies suggest that cardiovascular patients are more often reported with DDIs. The possiblereasonsbehindincludeolderage,multipledrugregimens,pharmacokineticorpharmacodynamics nature of drugs used in cardiology, and the influence of heart disease ondrug metabolism. A retrospective observational cohort study conducted was conducted with147 in patients. Majority of the study subjects were in the age group of 60 years and above(59%)andweremales(62%)thanfemales(38%). Mostofsubjectshadmultiplecomorbidities(72%),hypertension(11%),diabetesmellitus(6%)andCAD(5%). Atotalof704drug-drug interactions were identified. The majority of interactions were pharmacodynamics (58%) innature, having moderate severity (76%). Our research contributed to a better knowledge ofunderstandingaboutthecommonlyseencomorbidities,mechanismsandseverityofDDIsfromtheprescribedmedications.Alsohelpstoidentifytheriskof DDIsper drugsintheprescriptions.Thiscouldhelpourhospitalto improvethesafeandeffectiveuseofmedications.

KEY WORDS: Potential Drug -Drug Interactions (PDDI), Severity, Risk of DDIs per drugs,Lengthof hospitalstay,Inpatient Prescription(IP), DischargePrescription(DP).

I. INTRODUCTION
[1]Druginteractionsaredefinedasachangeinthewaya drugactsinthebodywhentakenwithcertainotherdrugs, herbalsorfoods,orwhentakenwithcertainmedicalconditions.Druginteractionsmaycausethedrugtobemore orlesseffectiveorcauseeffectsonthebody that are not expected. **Drug-drug interactions (DDIs)** occurs when two or moredrugsreactwitheachother.

DDIs may cause unexpected side effects. For example: interactions between sedativesand antihistamines can slow the reactions time thus making driving a car or operatingmachinerydangerous.

[2] MECHANISM PF DRUG INTERACTION

a)Absorption:	Example;
i. Inductionandinhibitionofdrugtransporterproteinssuchas P-gp	IncreasedabsorptionofDigoxinduetoinhibitionof P-gpby clarithromycin.
ii. Chelationorcomplexformation	Activatedcharcoalinhibitstheabsorptionofdabigatran.

b)Distribution	Cellmembranetransport tothesiteofaction
d)Clearance	Metabolism orexcretionofactivedrug
I. Metabolism	Example:
InhibitionofCYP450 enzymes	Increased plasma concentration of SimvastatinduetoinhibitionofCYP3A4byamiodarone,therebyincreasingtheriskformusclesymptoms.
InductionofCYP450enzymes	Reducedplasmaconcentrationofcyclosporinebyrifampicin,causinganincreasedriskoftransplantrejection.
II. Excretion	Example;
Changesinrenaltubularexcretion	Reducedexcretionofdigoxinduetospironolactone
Changesinrenalbloodflow	NSAIDscauseariseintheplasmaconcentrationof lithium.
4.Pharmacodynamic	Alteredeffect
Mechanism	molecularsignal(e.g.,receptor)
Mode	Physiologicaleffect

Table 1

AccordingtoWHOthenumberofcasesincardiovasculardepartmentwillincreasefrom29 million in the year 2000 to about 69 million cases in the year 2015. The potentialdrug-drug interactionincreasesasthe numberof concomitantdrug increases.Theincidence of drug interactions among the cardiac patients was more common thanpatientsof otherdepartments. [3]A study reported by Cruciol-Souza showed that overall frequencyof pDDIs was 49.7% in cardiology. [4] The prevalence of patients with potential drug-drug interactions were found to be 72.2%. Based on severity, the prevalence of major,moderate,andminorpotentialdrug-druginteractionsas25.1%,52.8%,16.9%,respectively ,also1.27%forcontraindication. [5]Thepercentageofdug-druginteractionswere higher in females compared to males (56.82% vs 43.18%). Drug-drug interactionswereobservedmoreintheagegroupof60years andabove(57.96%).Patientwithmorethan10prescribeddrugsdevelopeddrug-druginteractionsmorefrequently(58(65.91%)). Heparin (55(62.25%)) and Aspirin (42(47.72%)) were the most commondrugs responsible for drug-drug interactions. Bleeding was the commonest clinicalconsequence(N=76, (86.63%))found in study population. [6] Theincidence ofcardiovascular diseaseshassignificantlyincreasedinthe recentdecadesandconsideredasaleadingcauseofdeat

hsworldwide.StudiesfromseveralfieldsindicatethatDDIsaremorefrequentlyreportedincardiovascularpatients.Oldage,multiple-drugregimens,the pharmacokinetic or pharmacodynamic nature of drug, impact of heart disease on drugmetabolism are some of the potential causes.

Since DDIs are one of the most crucialcomponents of patient drug safety since they can render drug therapy ineffective, createunforeseen side effects, and change a specific medicine's mechanism of action and they arepredictable,treatable,and preventable.

Astudyhasbeenconductedwithanobjective;

1. Toidentify thecategory ofdrugs that causedsevereDDIs
2. To analyze and correlate the risk factors associated with DDIs (age, length of hospital stay,numberofdrugsinpastmedicationhistory,inpatientmedicationchartanddischargeprescription)in hospitalized patients.
3. ToidentifythepharmacokineticandpharmacodynamicDDIs

II. MATERIALS AND METHOD

A tertiary care facility served as the setting for this retrospective observational cohort study.This study consisted of 147 participants. Patients admitted under the cardiology department,those prescribed two or more medicines, those with many comorbidities, those who havepreviouslytakenmedication,andcaseswithserumcreatinine,prothrombintime,andINRweretheinclusioncriteria.Subjectsstayinginthehospitalforlessthan24 hoursandcasesthatwerereferredbyanotherdepartment t wereomitted.

Since this was a retrospective study, informed consent was not sought. Prior to the trial, IRBapproval from the hospital was obtained. The demographic information (age, sex, date ofadmission,dateofdischarge),comorbidities,pastmedicationhistory,serumcreatinine,prothrombintime, and INRwere collected fromthe medical records.

III. STATICAL ANALYSIS

DDIs were identified and categorized using Medscape data base version 8.3, Drugs.comversion2.12.1andRxListdruginteractionchecker.Descriptivestatisticswasusedtosummarize variable demographic parameters and study objectives. Discrete variables weretabulated and chi square test was used to analyze it. Continuous variables will be analyzedusingstudentTtestandZtest.ANOVAwereusedtoanalyzeinfluenceofindependentor dependent variable. A P value of <0.05 is considered as significant. Pearson Correlation wasused to correlate age, length of hospital stays, number of drugs –DDIs and risk of DDIs perdrug in IP and DP. The above data will be calculated using MS Excel 2010 and SPSS version20.

IV. RESULT AND DISCUSSION

[3,6] From the total of 147 cases, majority of the patients were males, followed by females.From that, the majority of the patients (59%) were in the age group of 60 years andabove, and was illustrated in Table 2, which is consistent with prior reports in theliteratures.

CHARACTERISTICS (n=147)	RELATIVE FREQUENCY(%)
GENDER	
MALE	62
FEMALE	38
AGE	
<40Years	3
40-60Years	38
>60Years	59

Table 2

Table 3 and 4 shows that out of 147 cases, 129 cases have DDIs in the inpatientprescription (IP) chart, 84 cases had DDIs in the discharge prescription (DP). From thatatotalof704DDIs weredetected.Majority oftheDDIs(63%)wereintheIPchart.

According to Straubhaar B [3] study, IP has lower DDIs (68%) than the DP (88.85%).Theauthorattributedthistothefactthat,upon admissionthenumberofdrugsperpatientwasfewerthanwhentheyaredischarged.Butinourstudysettingsweobtainedareverseofthisresult,i.e.IPhaveshownmoreD

DIs(63%),thantheDP(37%).Thismaybedue to increase in number of prescrip1tions per patient on hospital admission or may be duetoprescribingof drugswhicharepotentialtocausesuchDDIsinIPcompa redto DP.

PRESCRIPTIONS	DDI	NODDI	TOTAL
IP	129	18	147
DP	84	63	147
	N=213	N=81	

Table 3

TOTALDDIs	FREQUENCY	RELATIVEFREQUENCY(%)
IP	446	63
DP	258	37
	N=704	100

Table 4

Fromthetable5,itwasobservedthat,total446DDIsweredetectedfromIPs,fromthat173DDIsoccurredasaresultofpatients'pastmedicationsandtheremaining273DDIsresultedfromtheadministrationofmedicinesthatareprescribedduringthehospitalstay.

DDIs	FREQUENCY	RELATIVE FREQUENCY(%)
PMHVSIP	173	39
IPONLY	273	61
	N=446	100

Table 5

From the table 6, it is shown that total of 704 DDIs majority of DDIs observed were Monitorclosely in nature. [3, 7-9] In many of the studies, majority of the severity levels of DDIs arecategorizedasmoderateseverityormonitor closely,andour studyalsoshowsthe same.Very few studies show that the severity of majority of DDIs are serious in nature, this may bedue to variation in the prescribing pattern at various study settings. From that majority of theDDIs in IP shows severity category of monitor closely and get a similar result in case of DPsDDIsseverity.

SEVERITY	FREQUENCY	RELATIVE FREQUENCY(%)
IP+DP		
SERIOUS	109	15.48
MONITORCLOSELY	537	76.28
MILD	55	7.812
CONTRAINDICATED	3	0.43
	N=704	100
SEVERITYOFDDISAMONGIP		
SERIOUS	77	17.26
MONITORCLOSELY	338	75.78
MILD	30	6.73
CONTRAINDICATED	1	0.23

	N=446	100
SEVERITYOFDDIs AMONGDP		
SERIOUS	32	12
MONITORCLOSELY	199	77
MILD	25	10
CONTRAINDICATED	2	1
	N=258	100

Table 6

Thecategoryofdrugsthatcausesevere DDIswereidentifiedmorewithAnti-coagulants,othersandwasdepictedinfigure1. [10]AccordingtoastudybyAl-QeremW,thereportsshowthatthemostinteractingpotentialdrugcategoriesareAntiplateletandAnticoagulant agents (77.3%), followed by Antihypertensives (59.1%), Gastric acidsuppressants(31.1%),Hypolipidemicagents (20.9%), andAntibiotics (2.9%).
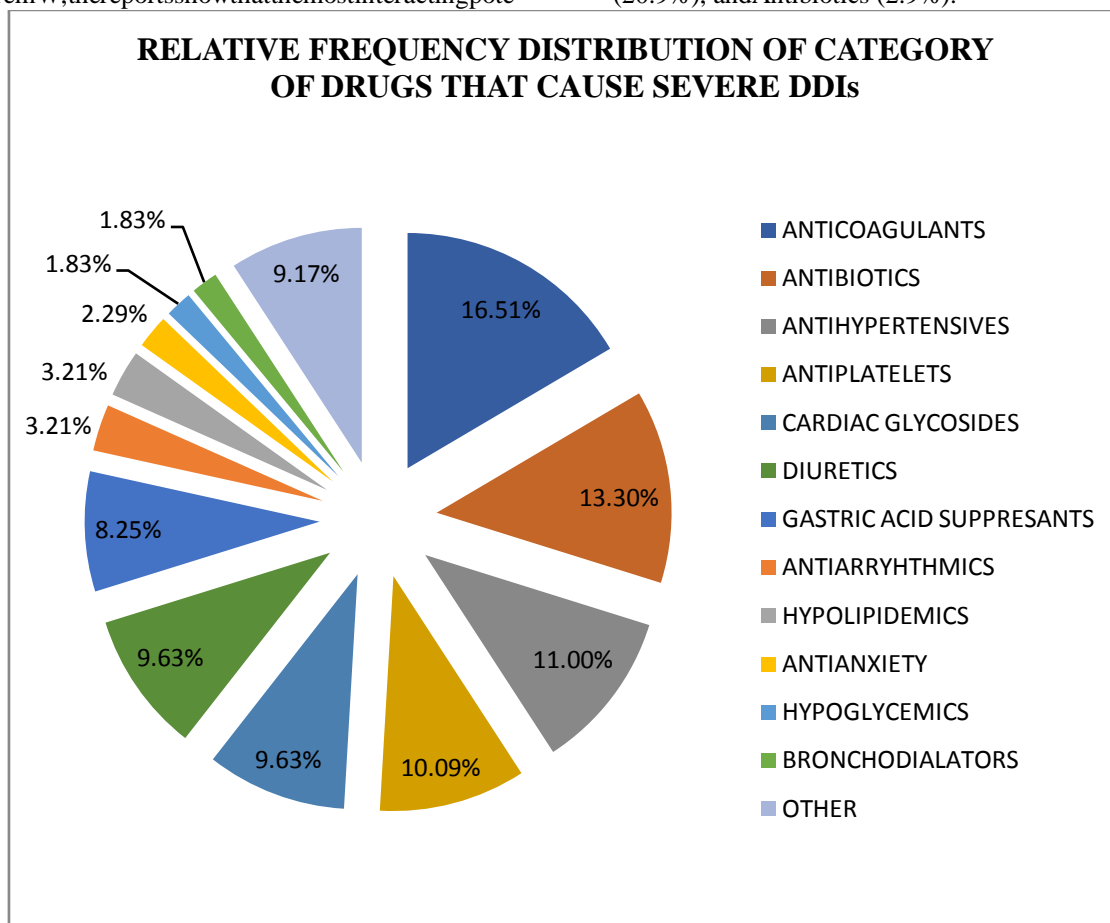

Figure 1

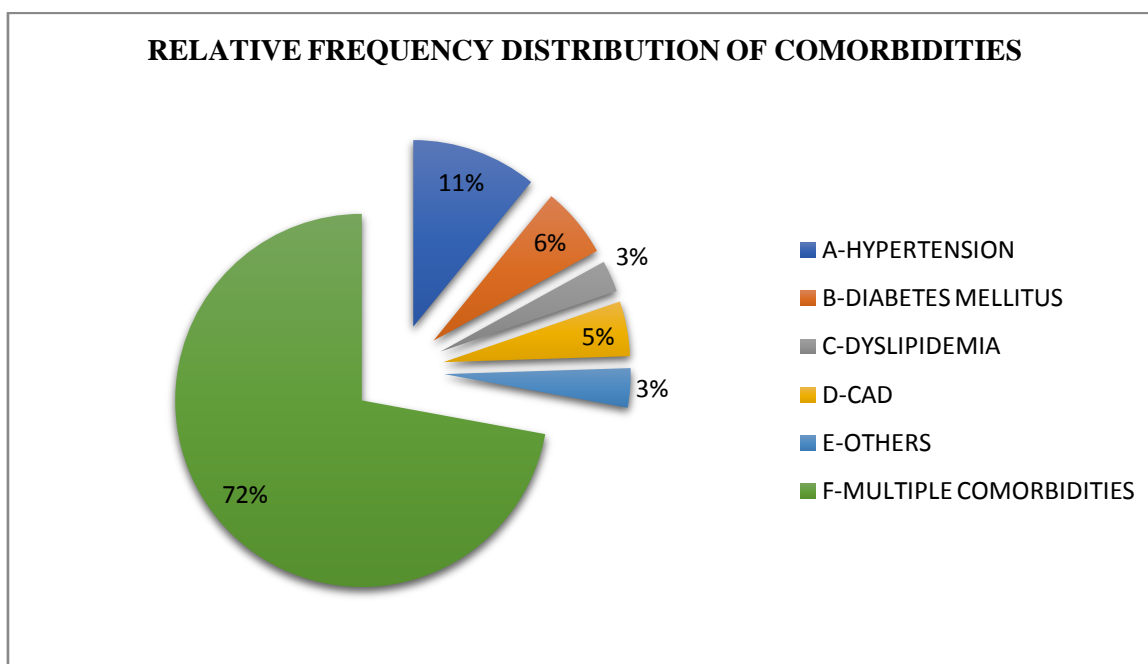Incaseofcomorbidities,majorityofthepatients(72%)hadmultiplecomorbidities.Andtheaboveresults weredepicted infigure2.

Figure 2

Upon analyzingthe length of hospital stay, majority of the patients were admitted to thehospital for five days. This is depicted in figure 3. [7] In a study by Shanbhag AD et al [7], theauthorshaveshown thatnumber ofhospital staywas morein between3-5days(62.2%).
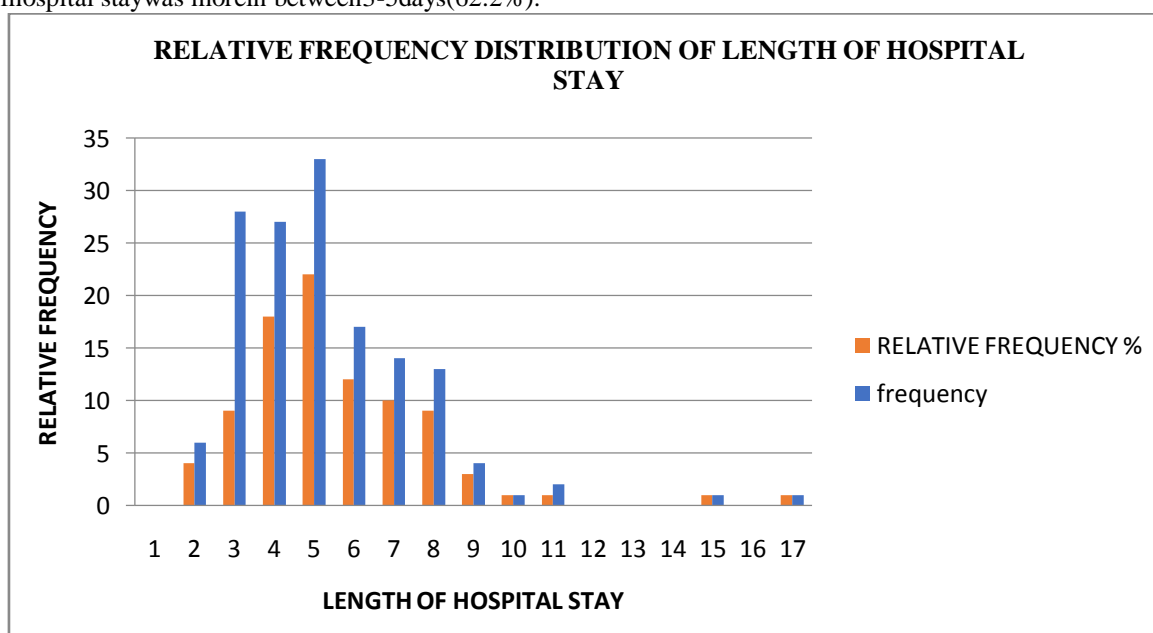

Figure 3

When we looked into the monitoring parameters such as Serum Creatinine and INR,majority of the patients had borderline levels of serum creatinine. And majority of thepatients had borderline INR. [13] Upon comparing to a study by Hosseinpoor Z et al.patients with increased levels of serum creatinine had a risk of QTc prolongation in thepresence of DDIs (10.7 %). [14] In our study, majority of the patients had a border line ofserum creatinine and which may make them more prone to the risk. In case of INR astudybyTeklayGetal,majorityofthepatientsonWarf

arintherapytheINRvalueslies between 2-3 (30.8%). Compared with the use of Warfarin alone, the concomitantuseofotherdrugswasassociatedwithincr easedriskofbleeding.Table-7representstherelativefrequency distribution ofSerum creatinineandINR.

MONITORINGPARAMETERS	FREQUENCY	RELATIVEFREQUENCY (%)
SERUMCREATININE		
≤1mg/dl	17	13.178
1.1-2mg/dl	94	72.868
≥2.1mg/dl	18	13.953
	N=129	100
INR		
≤0.9	39	27
1-1.9	106	72
≥2	2	1
	N=147	100

Table 7

From table -8 and 9 out of 704 interactions in total, most of the DDIs were non-beneficial innature. According to a study by H Rafiei et al [15], beneficial DDIs accounted for 33.1% of theoverallDDIs,whichwerelessthanharmfulDDIs interactions(66.9%).Our studyalsohasthesimilarresults,whichindicatesthatthe non- beneficialDDIsareverycommonintheprescriptionsan dhastobemonitoredcarefully.Mostcommonlyobserv edmechanismswere pharmacodynamic in nature. [4,5,7,8] MajorityoftheliteraturereviewsshowsthatthemechanismsofthemostoftheDDIsarepharmacodynamicinnat ure.Ourstudyalsoshowsthesame, which is samein caseofIPsand DPs whenweanalyzed separately.

DDIs	FREQUENCY	RELATIVEFREQUENCY (%)
TOTAL		
BENEFICIALDDIs	98	14
NON-BENEFICIAL DDIs	606	86
	N=704	100
Ips		
NON BENEFICIAL	386	87
BENEFICIAL	60	13
	N=446	100
DPs		
NON BENEFICIAL	220	85
BENEFICIAL	38	15
	N=258	100

Table 8

MECHANISM	FREQUENCY	RELATIVE FREQUENCY(%)
TOTAL		
PHARMACOKINETIC	209	41
PHARMCODYNAMIC	407	58
UNKNOWN	6	1
	N=704	100
Ips		
PHARMACOKINETIC	167	37
PHARMACODYNAMIC	273	61
UNKNOWN	6	1
	N=446	100
DPs		
PHARMACOKINETIC	123	47.675
PHARMACODYNAMIC	134	51.938
UNKNOWN	1	0.388
	N=258	100%

Table 9

One-way ANOVA analysis of variance was calculated and it showed no significantdifference between age group and average number of DDIs, [(F (5,143) = 1.1908,P=0.3166)].Andthere was nocorrelationexistbetweentheageandtheaverageDDIs,[r(40) =0.087877, p =0.580631].
[7] When compared to Shanbhang AD et al, they reported that rate of DDIs increasedwithage, with a pvalueof 0.05whereas wehave an opposite result.

And there exist a weak positive correlation of relationship between age and the DDIs[r=0.136,p=<0.01]
TheprobabilityofDDIsamongmalesandfemaleswasdonebyrandomlyselecting50casesofeachmalesandfemalesfromthe147casesusingMSExcelversion2010andaverageDDIs werecalculated from their 50 cases. ThereshowedthattheaverageofDDIswasseenmorein FemalescomparedtoMales,andwas illustrated in tables 10.

GENDER	RELATIVE FREQUENCY(%)	TOTALNO: OFDDIs (IP +DP)
FEMALES	56	296
MALES	44	235
	100	N=531

Table 10

Z test for mean was conducted by comparing the mean for the DDIs in Females (M=5.92, SD= 6.0266) to the DDIs in Males (M= 4.7, SD=3.688143). The result was notstatistically significant (Z=1.2209, p= 0.22210). There exists no difference in DDIsbetweenfemalesand males.
From table12, one-way ANOVA analysis of variance was conducted to find any significantdifferenceexistsbetweenlengthofhospital stayandaverageofDDIsinIPandfoundthattherewas no significant difference exist between different groups and average of DDIs [F (8,136) =1.4456, p=0.1830]. According to Shanbhang D A et al [7], their study shows a statisticalsignificancebetweenlengthofhospitalstayandDDIswithaPvalue=<0.001.Whencomparedtoour study, opposite result isobtained.

GROUPS	AVERAGE OFDDIs
2	1.666667
3	2.321429
4	2.961538
5	3.060606
6	3.588235
7	3.642857
8	2.5
9	7
11	4

Table 11

ANOVATABLE						
Sourceof Variation	SS	Df	MS	F	P-value	Fcrit
Between Groups	105.714851	8	13.21436	1.445687	0.183081	2.007119
Within Groups	1243.11274	136	9.140535			
Total	1348.82759	144				

Table 12
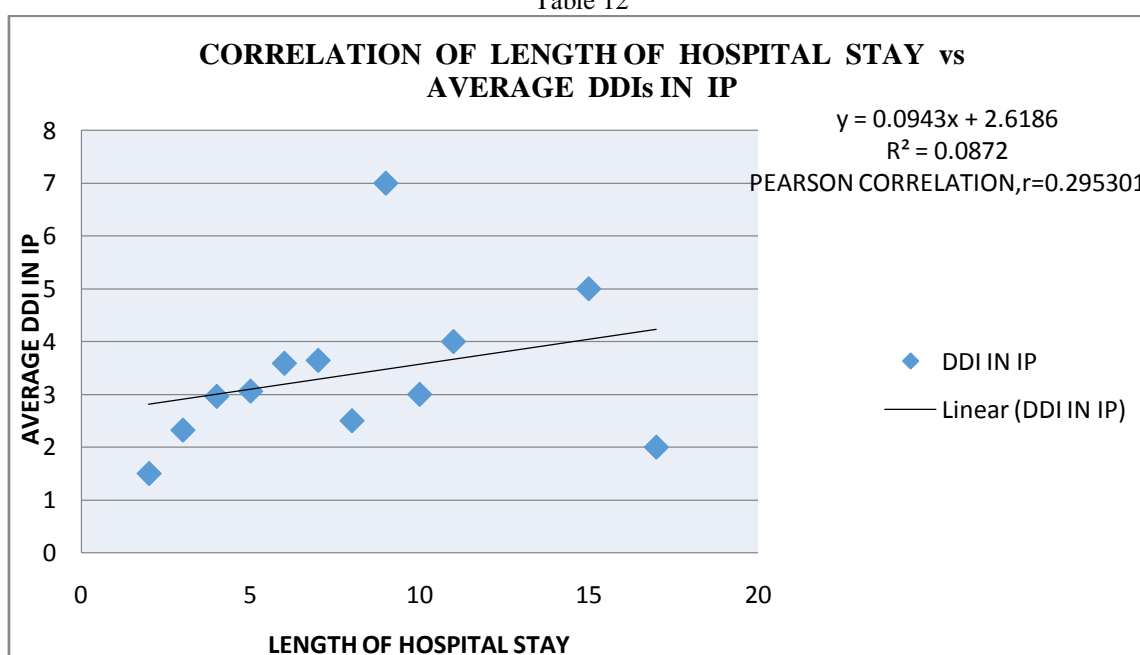

Figure 4

Figure4,showsaweakpositiveassociationbetweenthe lengthofhospitalstayandtheaverageDDIsinIP [r(10) =0.2953, p=0.35147].

[5] In comparison to a study by Mateti U V et al, the length of stay and DDIs were found tohave a significant linear correlation (r= 0.96; P <0.0001). But in our study, there were nosignificant correlation between the length of hospital stay and the DDIs. This may be becauseof difference in sample size of ours (147) when compared to Mateti U V et al with a samplesizeof600.

One-wayANOVAanalysisofvariancewasusedtofindwhet heranysignificantdifferenceexistbetweennumberofd rugsandaverageDDIsinIPsandDPs,thereshowednosi gnificantdifferencebetweenthenumberofdrugsinthep rescriptionsandaveragenumberofDDIsinIP[F(19,12 1)=1.4645,p=0.110].Andfrom figure 5 there shows a weak positive correlation between the number of prescriptions in IP and the average DDIs in IP. [r (24)=0.1899, p=0.3441]
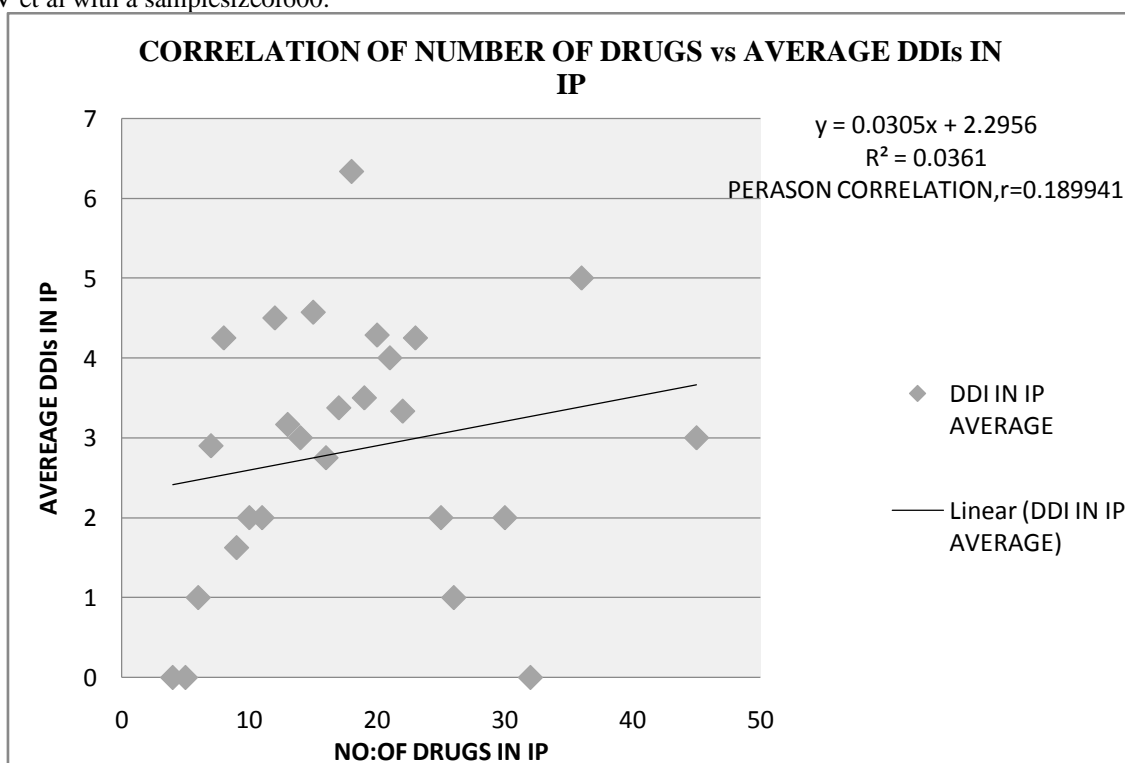

CORRELATION OF NUMBER OF DRUGS vs AVERAGE DDIs IN IP

$y = 0.0305x + 2.2956$
$R^2 = 0.0361$
PERASON CORRELATION,r=0.189941

Figure 5

Inourstudy,therewerenosignificantrelation shipbetweenthenumberofprescriptionand the number of DDIs in IP, and the result shows only a weak positive correlationbetween them. [16] This differs from the results of Jain S et al study, there it shows apositive correlation between the number of drugs prescribed and the DDIs (r=0.788,p<0.001) in the hospitalized cardiac patients. This could be as a result of rationalprescribingand patient monitoring.

In case of DPs, from table-14, there showed a significant difference exist between the numberof drugs and average number of DDIs in DP [F (15,127) =4.9818, p ≤ 0.001] With a strongpositive correlationbetweenthenumber ofprescriptionsinDPandtheaverageDDIinDP.[r(18) = 0.9102, p= <0.001], it is observed that as the number of drugs in DP increases the riskofDDIalso increases.

GROUPS	AVERAGEOF DDIs
2	0
3	0.75
4	0.444444
5	0.25
6	1
7	1.357143
8	1.411765
9	2.647059
10	1.5
11	1.625
12	2.571429
13	4.5
14	4.25
15	3.333333
16	7.5
17	6.5

Table 13

ANOVATABLE						
Sourceof Variation	SS	Df	MS	F	P-value	Fcrit
BetweenGroups	289.8524	15	19.32349	4.981807	1.32E-07	1.745816
Within Groups	492.6091	127	3.878812			
Total	782.4615	142				

Table 14

This result is comparable to the study by Shangbhang AD et al [7] which shows astrongpositiverelationshipwithapvalue<0.001byA NOVA,aswell asalinearcorrelation between the number of drugs administered per patient and total DDIs[r=0.620,p=<0.01][5].Thismaybeduetolessmon itoringofdischargeprescriptions of the patients by the prescriber. It indicates the need of moreinvolvementin monitoring theDPs by theClinicalPharmacists.
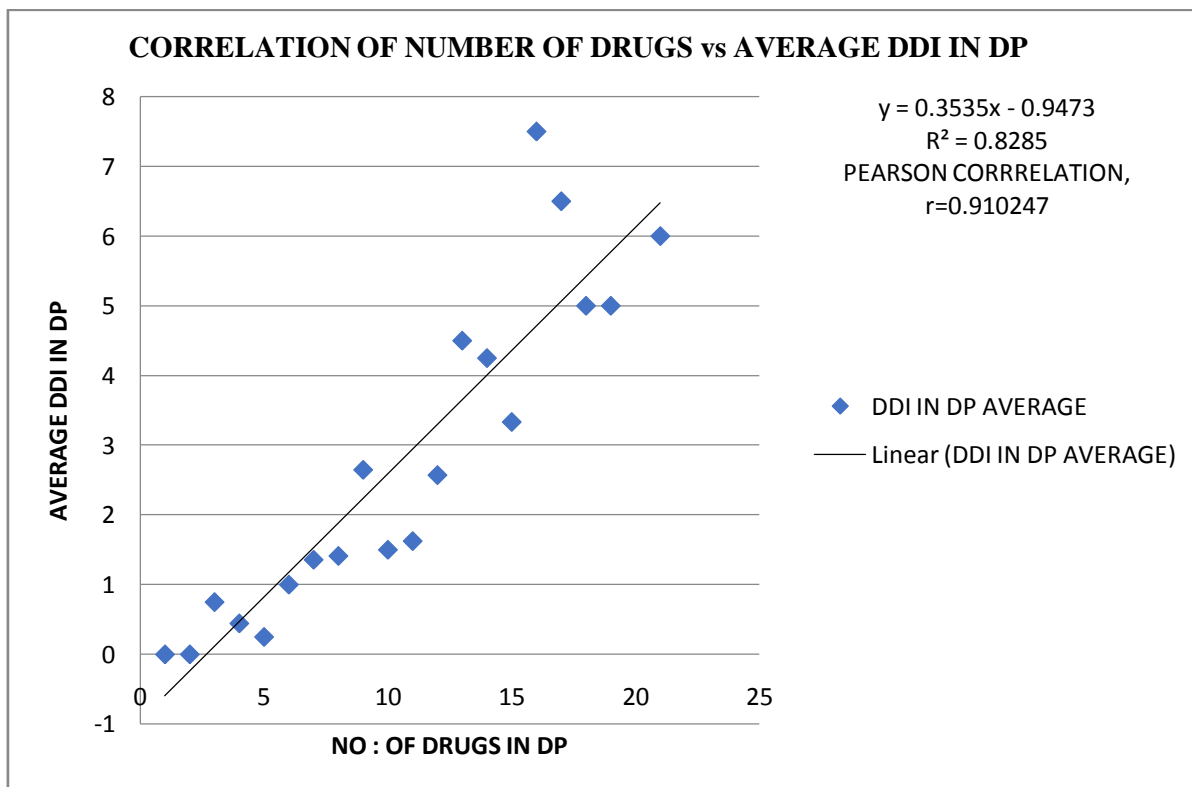
Figure 6

For comparing the number of DDIs in IP and DP, the chi square test of independencewas used and itrevealed a significant difference exist between the DDI in IP and DP,χ^2 (1, N=147) = 34.507 p = <0.001). As a result, Incidence of DDIs in IP vs DP, IP hasmore DDIs than DP. It indicates the need of close monitoring of the prescriptions by amultidisciplinary health care team with the involvement of Clinical Pharmacist will beusefulto achievethis outcome.

OBSERVED	DDI	NO DDI	TOTAL
NO:OF PRESCRIPTION INIP	129	18	147
NO:OF PRESCRIPTION INDC	84	63	147
TOTAL	213	81	294

Table 15

For obtaining a statistical result from table-16, Z test for mean was conducted bycomparing the mean for the DDI in IP (M= 3.0340, SD= 3.050) to the DDI in DP (M=1.7551, SD= 2.3773). The result was statistically significant (Z=4.0090, p=<0.001).Thereexists adifferencein DDIbetweenIP andDP.

ZTest:Two SampleforMeans		
	AVERAGEDDIsIP	**AVERAGEDDIsDP**
Mean	3.034013605	1.755102041
KnownVariance	9.3075	5.6519
Observations	147	147
HypothesizedMean Difference	0	
Z	4.009055739	
P(Z<=z)one-tail	3.0481E-05	
zCriticalone-tail	1.644853627	
P(Z<=z)two-tail	6.0962E-05	
zCriticaltwo-tail	1.959963985	

Table 16

RiskofDDIsperdrugwasusedtoidentifytheDDIsinbothIPsandDPs.Figure 7, shows that risk of DDIs in IP was more with prescription containing 8drugsfollowedbyprescriptioncontaining7drugscomparedtootherprescriptions.Formostofthedrugs,riskso fDDIsperdrugislessthan0.2;asthenumberofdrugsin theprescriptionsincreasesesitis observedthattheDDIriskperdrugreducesanditmaybe duetheclosemonitoringoftheprescriptionscontaining more number drugs, whereas prescriptions containing few numbers ofdrugs are monitored less by the Prescribers and the Clinical Pharmacists as theirinvolvementsareless inmaking interventions withless numbers of drugs.

In case of risk of DDIs per drug in case of DPs from Figure 8, it shows that risksof DDIs per drug is more with prescription containing 16 drugs followed by 17drugs when compared to other prescriptions. Most of the prescriptions shows ariskofDDIsperdrugandismorethan0.2;asthenumber ofdrugsintheDPsincreases it is observed that the DDI risk per drug increases. This may be duetoless the monitoring of prescriptions by the Prescribers and less involvement ofClinicalPharmacist interventions of theDPs.

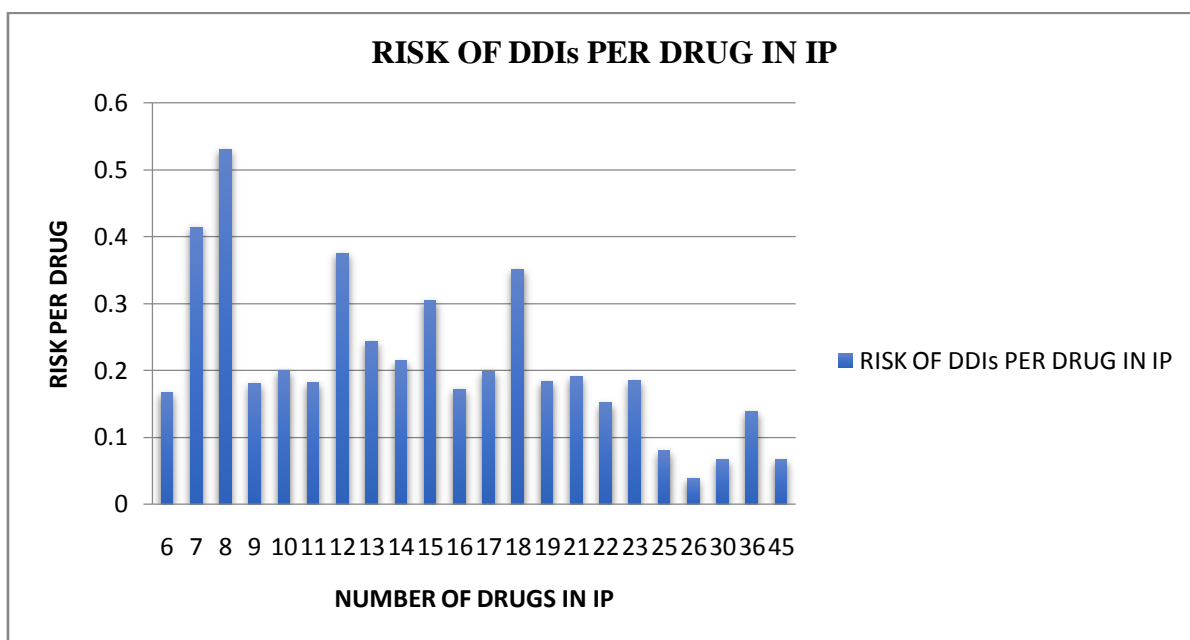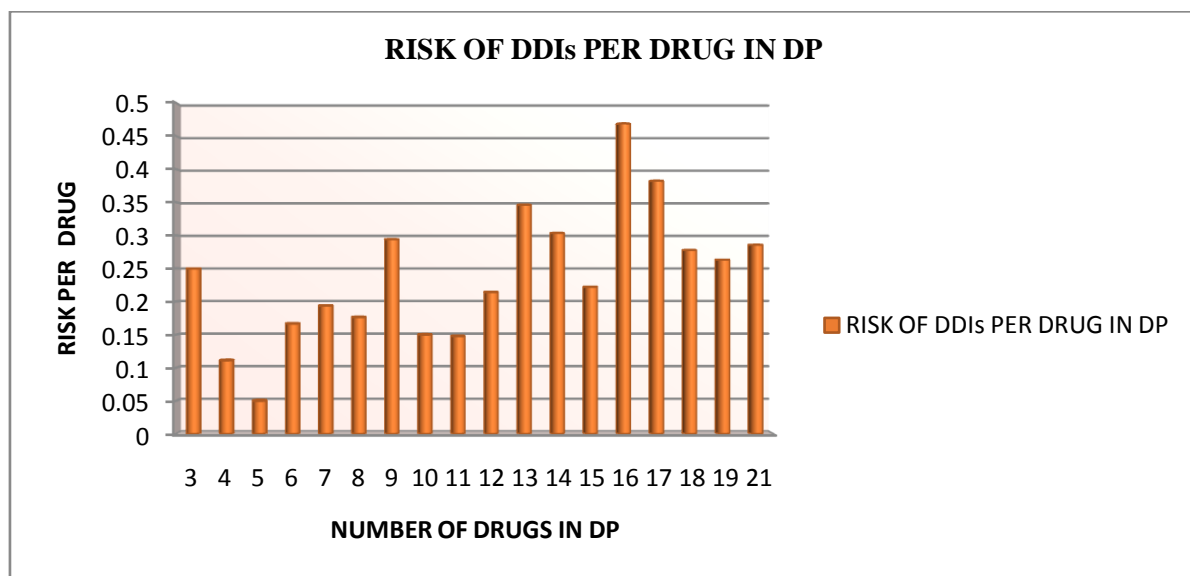Figure 7

Figure 8

Pearson correlation was used to find the correlation between number of drugs and riskofDDIs.Thereshowsweaknegativecorrelationexistsbetweennumberofdrugsvsriskof DDIs in IP (r (26) = -0.19311, p value=0.325) and are statistically not significant,there is a moderate-positive correlation or association exists between number of drugsinDP and risk ofDDIs (r(17)= 0.6919, p value=0.001031)and was depicted infigure 9. There shows that risks of DDIs per drug increases with drugs in prescription in amoderate level. This may be due to less involvement of the healthcare professional inmakingintervention for theDP.
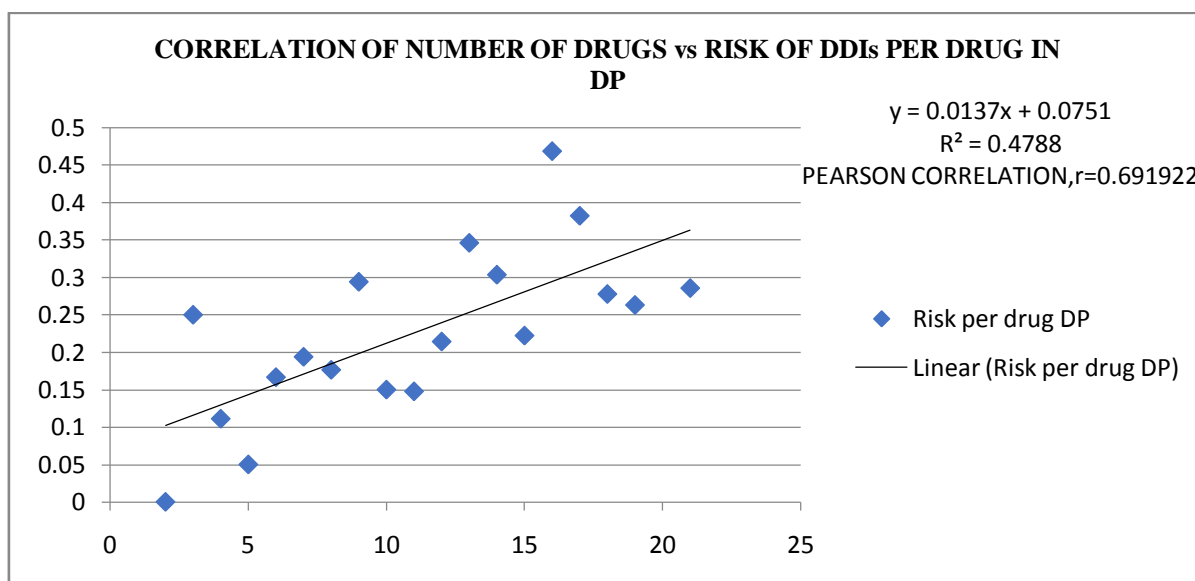
Figure 9

On comparing the risk between IPs and DPs, high risks of DDIs per drug is seen with IPs (0.53125 per drugs), with prescription containing 8 drugs, because of prescribing drugs which has the potential to cause DDIs but are prescribed to stabilize the patient who has been hospitalized. Due to the less monitoring of prescription containing few numbers of drugs by Prescribers. In DPs, risk is higher with prescriptions containing 16 drugs and was due to less monitoring of the prescriptions by the prescriber and involvement of clinical pharmacists in DP monitoring.

A t test, results shows that there is no significant difference between risk of DDIs per drug in IP (Mean=0.2606, SD=0.11027) compared to DP (Mean=0.2595, SD=0.09186) with t(27) = 0.02933, p= 0.97681. So, in both IP and DP close monitoring of the prescription is required and also involve the Clinical Pharmacist in those areas of clinical practice.

V. CONCULUSION

The easiest way to reduce high frequency of prescription of drugs with potential drug interaction is to close monitor the number of medicines prescribed with the involvement of multidisciplinary teams. Nevertheless, sometimes it is difficult to reduce the number of drugs prescribed for patients with multiple chronic conditions; therefore, to lower the frequency of potential interactions it could be necessary to make a careful selection of therapeutic alternatives, and in cases without other options, patients should be continuously monitored to identify adverse events.

LIMITATIONS

1. It was a retrospective study.
2. This study was conducted in a short term duration, having small sample size and conducted in a single center.
3. Patients are studied only while they are hospitalized to cardiology department. Therefore, any complications occurring after patients' discharge from their wards were not documented.

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