ASSESSMENT OF PHARMACOTHERAPY, POTENTIAL DRUG-DRUG INTERACTIONS AND MANAGEMENT STRATEGIES IN CRITICAL CARE UNITS AT TERTIARY CARE HOSPITALS OF PESHAWAR, PAKISTAN

Ph.D Thesis

By

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University of Peshawar, Peshawar, Pakistan

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Certificate of Approval

This thesis, entitled, "**Assessment of pharmacotherapy, potential drug-drug interactions and management strategies in critical care units at tertiary care hospitals of Peshawar, Pakistan**" submitted by **Mr. Faisal Shakeel** is hereby approved and recommended as partial fulfillment for the award of degree of Doctor of Philosophy in Pharmacy.

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TO

MY PARENTS

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SUMMARY

Pharmacotherapy is to study the effect, determine appropriate use and dosage of drugs. To achieve optimum results of drug therapy, considerations to both drug and patient related parameters must be given. However, drug use can also lead to various drug related problems of which potential drug- drug interactions (PDDIs) are very significant. Factors like polypharmacy further increase the risk for potential drug-drug interactions, specially in critical care units where the critical state of the patient along with co-morbidities, futher increases the risk of PDDIs. The study was conducted in the critical care units of Lady Reading Hospital, Khyber Teaching Hospital, Hayatabad Medical Complex and Northwest General Hospital and Research Center Peshawar, Pakistan.

In the surgical intensive care unit (SICU) of the four hospitals, a total of 860 patients were evaluated using Micromedex databases and an average of 45.4% patients were presented with PDDIs which were attributed to a total of 162 PDDIs from 38 drug pairs. Of these PDDIs, an average of 34.1% were of moderate and 61.9% of major severity, 26.2% were of good while 63% of fair documentation. The onset of PDDIs of all the hospitals averaged 35.8% and 57.9% as delayed and unknown respectively. Of the total PDDIs 44.5% were of unknown mechanism. A significant association was found between number of interactions and 5 or more prescribed drugs ($p = 0.000$), and in KTH between number of interactions and gender ($p = 0.001$) while in the rest of the hospitals an insignificant associations was found between number of interactions and gender and duration of stay. To compare the means of PDDIs, one way ANOVA was applied which resulted in a significant difference between the private and government hospitals ($p = 0.000$). The interacting drug pairs which had the potential for a significant clinical effect on the patients condition included valproate + imipenem/meropenem, enoxaparin +

ketorolac, aspirin + enoxaparin, nimodipine + valproate, ketorolac + nimodipine, phenytoin + nimodipine, dexamethasone + phenytoin and atracurium + dexamethasone.

Of the total 830 patients evaluated in the medical intensive care units (MICU) of the four tertiary care hospitals, an average of 39.2% were presented with a PDDI. Of these 71 drug pairs resulted in 175 PDDIs. Most of the PDDIs encountered were of major (47.6%) and moderate (42.7%) severity while good (38.2%) and fair (45.5%) documentations were frequently encountered. Of the total PDDIs 47.48% were of delayed and 40.18% were of rapid onset. Pharmacokinetic type of PDDIs were prevalent among all, averaging 52.4% while pharmacodynamic type were only 38.4%. Metabolism was the prevalent mechanism and caused an average of 39.5%, while synergism caused 34.2% PDDIs. The association between number of interactions and 5 or more prescribed drugs was highly significant ($p = 0.000$), and in LRH and KTH the association between number of prescribed drugs and gender was also significant, $p = 0.012$ and $p = 0.035$, respectively. While the rest of the hospitals had an insignificant association between number of interactions and duration of stay and gender. One way ANOVA showed a significant difference in the means of PDDIs between NWGH & RC and HMC ($p = 0.042$), and between KTH and LRH & HMC ($p = 0.000$). The drug pairs having a significant clinical effect included clarithromycin + carbamazepine, aspirin + enoxaparin, clopidogrel + omeprazole, hydrocortisone + moxifloxacin, aspirin + dexamethasone, rifampin + dexamethasone, acyclovir + phenytoin/valproate, rifampin + valproate, carbamazepine + metronidazole, nimodipine + valproate and dexamethasone + phenytoin.

A prevalence of 95.3% PDDIs was encountered in a total of 1030 patients admitted to the cardiac intensive care units (CCU) of the four hospitals. A total of 92 pairs attributed to the 1165 PDDIs encountered in this unit. Of these PDDIs, an average of 52% were

of moderate and 46.3% of major severity, 50.5% were of good while 39% of fair documentation. The onset of PDDIs of all the hospitals averaged 23.8% and 58.5% as delayed and unknown respectively. Of the total PDDIs 72.9% were of pharmacodynamic nature, and in terms of mechanisms, synergism was the most prevalent (46.5%). A significant association was found between number of interactions and number of prescribed drugs in LRH (p = 0.005), KTH (p = 0.047), HMC (p = 0.002) and NWGH & RC (p = 0.000). While in all the hospitals an insignificant associations was found between number of interactions and gender and duration of stay. To compare the means of PDDIs, one way ANOVA was applied which resulted in a significant difference between the private and government hospitals (p = 0.000). The clinically significant interacting drug pairs included aspirin + enoxaparin, ramipril + spironolactone, clopidogrel + omeprazole/esomeprazole, digoxin + spironolactone, aspirin + betablockers, aspirin + furosemide, aspirin + spironolactone, aspirin + nitroglycerin, atorvastatin + clopidogrel and digoxin + furosemide.

In the stroke unit (SU) of NWGH & RC, a total of 240 patients were evaluated for PDDIs and a prevalence of 70.8% was recorded, which were due to 89 drug pairs resulting in a total of 474 PDDIs. Moderate severity (54%), good documentation (57%), delayed onset (34.6%) and pharmacodynamic type (55.1%) PDDIs frequently occurred, while synergism (32.9%) was the mechanism of most of the PDDIs. A significant association was found between number of PDDIs and 6 or more prescribed drugs (OR = 6.056; 95%CI = 3.247-11.293; p = 0.000) while the clinically significant drug pairs included aspirin + enoxaparin, ramipril + spironolactone, clopidogrel + rabeprazole, aspirin + furosemide, aspirin + spironolactone, aspirin + dexamethasone, aspirin + carvedilol, aspirin + amlodipine, aspirin + hydrochlorothiazide and furosemide + ramipril.

LIST OF ABBREVIATIONS

ACE:	Angiotensin Converting Enzyme
ACS:	Acute Coronary Syndrome
ARBs:	Angiotensin Receptor Blockers
C/S:	Cesarean section
CABG:	Coronary Artery Bypass Graft
CCU:	Cardiac Intensive Care Unit
CI:	Confidence Interval
COPD:	Chronic Obstructive Pulmonary Disease
COX-2:	Cyclo-Oxygenase 2
CSF:	Cerebrospinal Fluid
CVA:	Cerebrovascular Accident
GCP:	Good Clinical Practice
GIT:	Gastrointestinal Tract
HMC:	Hayatabad Medical Complex
HMG-CoA:	Hydroxyl Methyl Glutaryl Co-A
ICU:	Intensive Care Unit
KTH:	Khyber Teaching Hospital

LRH:	Lady Reading Hospital
MAO:	Monoamine Oxidase
MI:	Myocardial Infarction
MICU:	Medical Intensive Care Unit
NSAIDs:	Non-Steroidal Anti-inflammatory Drugs
NWGH & RC:	Northwest General Hospital & Research Center
OR:	Odds Ratio
OTC:	Over the Counter
P-gp:	P-glycoprotein
PDDIs:	Potential Drug-Drug Interactions
PPI:	Proton Pump Inhibitors
RTA:	Road Traffic Accidents
SICU:	Surgical Intensive Care Unit
SSRI:	Selective Serotonin Reuptake Inhibitor
SU:	Stroke Unit
UK:	United Kingdom
USA:	United States of America

Chapter 1:

Introduction

1 INTRODUCTION

1.1 The concept of pharmacotherapy

Evolution in the field of medicine has led to the discovery of newer drugs to treat and prevent diseases. However, with such remarkable improvements it has become very difficult for the health care professional to keep up with this growing knowledge, especially knowledge related to drugs. Newer drugs are being discovered and approved frequently for the treatment and prevention of various diseases, so keeping up to date with this ever increasing flow of knowledge and implementing this knowledge aptly for the benefit of the patient is extremely difficult and time consuming. Multiple drug therapy is now the mainstay for many chronic illnesses, complicating the situation even more. This is why the concept of pharmacotherapy is so critical.[1]

Pharmacotherapy is "the correct use of drug therapy for the purpose of preventing and treating a disease or illness." Achieving this goal becomes difficult at all times due to each patients uniqueness. Consideration should be given not only to drug related parameters but also to the patient related parameters like age, gender, ethnicity, socioeconomic status, personal and spiritual beliefs, possible genetic variations, comorbidities, and other medications.[2,3]

Thus pharmacotherapy involves studying the effects of drugs, determining the appropriate use and dosage of drugs. Currently, drug therapy is the most frequent and cost effective medical intervention performed by a medical practitioner. The total drug consumption, thus, is mainly due to the prescribed drugs and partly due to over the counter (OTC) drugs and nutritional supplements. The use of drugs has increased over time and the number of drugs per prescription has also risen, termed as polypharmacy.

This may be beneficial for some patients but in others it is a cause of irrational prescribing and excessive drug use. All drugs have some unwanted effects like adverse drug reactions and drug-drug interactions, polypharmacy, thus, increases this risk.[4,5]

1.2 Problems with drug use

Prescribing, dispensing and administration errors along with patient non-compliance are some of the problems associated with the use of drugs which not only reduce the efficacy of drugs but also results in increased mortality and morbidity.[6] A systematic review conducted in UK reported that only 4-21% of the patients in primary care settings achieved optimum results from their drug therapy.[7] Similarly, a 12 month cohort study in an ambulatory setting reported 1523 adverse drug events, 27.6% of which were preventable adverse drug events.[8]

1.3 Drug-drug interactions

The most common preventable error is drug-drug interactions.[9] Drug interaction is a change in the pharmacological activity or potency of one drug by the simultaneous administration of another drug. This may result in the amplified or weakened effect of a drug or a completely new effect, not expressed when the drug is used alone. [10]

1.4 History of drug interactions

The concept of drug interactions evolved in the 1960s where it was found that drug may interact with substances simultaneously administered with it. In that case it was food. Severe fatal hypertension was reported in patients taking monoamine oxidase inhibitors (MAO) and food containing cheese.[11,12] Later on it was found that MAO also interacted with psychotropic drugs.[13] Animal experiments in the 1960s also revealed that many

drugs interact with the metabolism of other drugs. In 1963, it was reported that sulphaphenazole inhibited the metabolism of tolbutamide resulting in hypoglycemia. The era of 1970s saw many reports regarding drug interactions. Publications related to drug interactions in Medline rose from 43 to 1400 between 1970 and 1980. In the coming years studies on drug interactions grew interest and concern and many drug-drug interactions were reported.[14]

1.5 Importance of drug-drug interactions

Complex pathological conditions make it necessary to prescribe a multiple drug regimen (polypharmacy), therefore, it is practically impossible for prescribers to remember the drugs having potential drug-drug interactions. The resulting consequence is that the drug interaction may cause a serious adverse effect or alter the therapeutic effect of another drug.[15,16] For example, use of hydroxyl methyl glutaryl Co-A reductase (HMG-CoA reductase) inhibitors with niacin, erythromycin, gemfibrozil or itraconazole can cause rhabdomyosis,[17,18] Selective serotonin reuptake inhibitors (SSRIs) when used with tramadol causes serotonin syndrome and increased potential for seizures,[19] SSRIs use with zolmitriptan may also cause serotonin syndrome,[20] increased potassium level due to the use of Angiotensin Converting Enzyme (ACE) inhibitors with potassium sparing diuretics may cause arrhythmias,[21] risk of bleeding may be increased when warfarin is used with aspirin and Non-Steroidal Anti-inflammatory Drugs (NSAIDs),[22,23] lithium toxicity may occur when lithium is used with NSAIDs or diuretics.[24.25]

Increase in therapeutic levels of carbamazepine may be caused when it is used with cimetidine, erythromycin and fluconazole.[26,27] Similarly, phenytoin levels are increased

when it is used with rifampin.[28] The effectiveness of oral contraceptives may be decreased when used with rifampin or torglitazone,[29] tricyclic antidepressant levels may increase when used in combination with SSRIs.[30]

Avoidance of alterations in therapeutic effects and increase in the seriousness of adverse effects due to drug interactions becomes imperative as they may have drastic effects on the health of the patients.

1.6 Types of drug-drug interactions

Many types of drug-drug interactions exists, but majorly they can be classified into pharmacodynamics and pharmacokinetic.

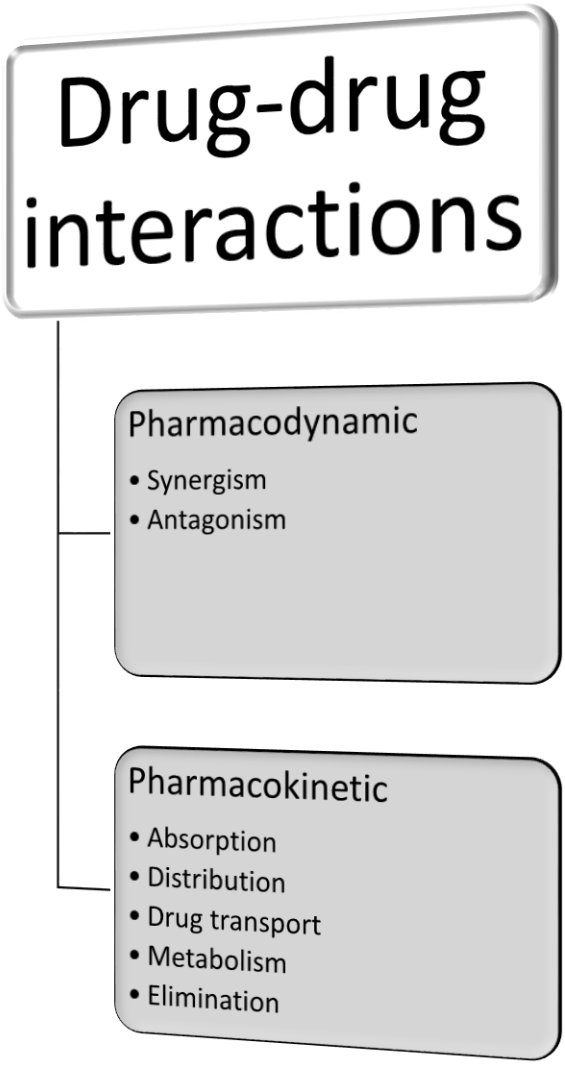

Figure 1.1 classification of drug-drug interactions

1.6.1 Pharmacokinetic drug interactions

Pharmacokinetic drug interactions involves modification in the drugs absorption, distribution, metabolism and elimination. These interactions can be measured by quantification of serum concentrations, half-life of the drug, free and bound drug, amount and rate of drug eliminated. Following are the mechanisms involved in pharmacokinetic drug interactions.[10]

1.6.1.1 Absorption

Oral route is most commonly used for drug administration. Absorption of drug from the gastrointestinal tract (GIT) is dependent on factors like pH, gastrointestinal motility, surface area for absorption, and blood flow to the absorption site, physical state of the drug and pKa of the drug. These factors may reduce or delay the absorption of drugs, for example reduced absorption of antidiabetic drugs may result in uneven levels of blood glucose leading to uncontrolled diabetes, whereas delayed absorption of antibiotics may result in uneven plasma concentrations. Drug interactions caused by changes in absorption do not usually cause clinically detectable adverse effects unless the drug has a short half-life or require rapid achievement of peak plasma concentrations, for example analgesics and hypnotics.[31]

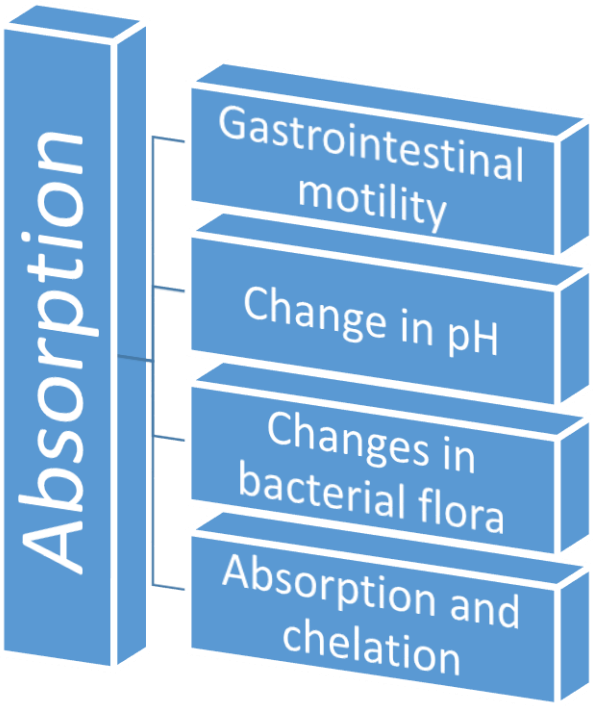

Figure 1.2 Mechanisms responsible for change in absorption

1.6.1.1.1 Gastrointestinal motility

Alterations in the rate of drug absorption occurs with change in gastrointestinal motility, however the extent of absorption remains unaffected. Increase in the rate of gastric emptying results in the rapid absorption of drugs with higher dissolution rates. Co-administration of cyclosporine and metoclopramide resulted in 30% increase in cyclosporine plasma concentration. However, for drugs which are slowly dissolved the rate of absorption decreases. Co-administration of digoxin and metoclopramide resulted in 20% decrease in digoxin plasma concentration.[10] Ranitidine causes reduced absorption of aspirin when used concurrently resulting in decreased plasma levels and effect of aspirin.[32]

1.6.1.1.2 Change in pH

Drugs are absorbed in un-ionized form by passive trans-cellular mechanisms. Changing the pH of gastrointestinal tract changes the fraction of drug available for absorption. According to the pH partition theory, weak bases are better absorbed at pH values higher than the pKa while weak acids are better absorbed at pH values lower than the pKa, so changing the pH of GIT will change the rate and extent of absorption. Ketoconazole is a drug which requires acidic environment for dissolution and administering it with antacids, proton pump inhibitors or H2 receptor antagonist may reduce its absorption.[33]

Drugs are either weak acids or weak bases thus alteration in absorption occurs with changes in gastrointestinal pH. Weak bases are better dissolved in gastric fluids as compared to intestinal fluids, whereas the opposite is true for weak acids. So changes in the pH of gastrointestinal tract with the use of drugs like antacids, which raise the

pH of the GIT may inhibit the absorption of weak basic drugs while enhance the absorption of weak acidic drugs.[34]

1.6.1.1.3 Changes in bacterial flora

Drugs which are not completely absorbed in the small intestine, or are secreted back into it are affected by changes in bacterial flora following antibiotic administration. Reduction in the absorption of oral contraceptives occurs with concurrent administration of antibiotics because the bacteria needed for enterohepatic recirculation of estrogen are depleted by this interaction.[35] Antibiotics may disrupt the bacterial synthesis of vitamin K causing an increase in the anticoagulant effect of warfarin, leading to an increased risk of bleeding.[36]

1.6.1.1.4 Adsorption and chelation

Drugs with large surface area like antacids and charcoal may bind with other drugs to form insoluble complexes or chelates. These complexes delay or reduce the absorption of drugs. Ciprofloxacin forms insoluble chelates when administered orally with aluminum, calcium, zinc or magnesium containing antacids, iron and other divalent or trivalent cations. Peak plasma levels of captopril have been reported to be decreased by 50% with the concurrent use of antacids.[37,38] The absorption of anticonvulsants like phenytoin and gabapentin is also decreased with the simultaneous use of antacids.[39,40] Charcoal and ion exchange resins like cholestyramine and colestipol reduces the serum concentration of drugs like thyroid hormones, diuretics, anticoagulants and digoxin by disrupting their absorption.[41]

1.6.1.1.5 Drug transport

The importance of transport molecules in drug interactions has been established recently. The presystemic clearance of drugs follows two mechanisms.

First is by P- Glycoprotein (P-gp) which is present on the enterocytes and hepatocytes. It reduces the absorption of drugs by ejecting drugs which have been diffused through the intestinal epithelial barrier and act as a detoxification pump. Secondly, CYP3A4 enzyme is also present in the intestine and it causes metabolism of drugs like antifungals.

Rifampin is an inducer of P-gp present in the gut lining and causes the ejection of digoxin into the gut thereby decreasing the digoxin plasma concentration. While verapamil is an inhibitor of P-gp and increases digoxin plasma concentration.

P- Glycoprotein is also present in the epithelial cells of the blood brain barrier and effects the distribution of drugs into the brain. Cerebrospinal fluid (CSF) concentrations of ritonavir have been reported to be increased by ketoconazole.[42]

1.6.1.2 Distribution

Mostly drugs have high affinity for protein in blood. Basic drugs bind to alpha-1 acid glycoprotein, while acidic and neutral drugs bind to albumin in plasma. Upon saturation of albumin, these drugs bind to lipoproteins.[43] Drug-drug interaction at this level occurs when two drugs having high affinity for plasma protein are given concomitantly. The drug having higher affinity will displace the drug having lower affinity, increasing its free or unbound concentration in blood thus making it available to drug receptors hence increasing its pharmacological action.

This is particularly significant when the drug being displaced is highly protein bound, has a small volume of distribution, narrow therapeutic index or rapid onset of action. For example warfarin is displaced by phenylbutazone, resulting in the increase in prothrombin time and risk of bleeding. Similarly, phenytoin may also be displaced from its binding sites and hepatic metabolism inhibited by valproic acid, resulting in increase in phenytoin plasma levels and toxicity. In Intensive care units (ICU), cardiac toxicity after tricyclic antidepressants overdose can be reduced by administering sodium bicarbonate as it changes the volume of distribution of the tricyclic antidepressants. [31]

Recently, studies have shown that although in-vitro displacement of drugs is a major mechanism for drug-drug interaction. However, in the body these effects are so well buffered that the drug-drug interaction may not be clinically significant. Apart from this many drug-drug interactions which were believed to be caused due to changes in drug distribution are also affected by other mechanism and distribution alone is not the significant mechanism. This does not mean that changes in protein binding has no effect on drugs and are not important for therapeutic drug monitoring.[31]

1.6.1.3 Metabolism

Alteration in the metabolism affects the action and duration of many drugs. Most of the clinically significant drug-drug interactions are due to changes in metabolism. During metabolism, lipid soluble compounds are converted into polar and water soluble compounds facilitating and enhancing their excretion through urine and bile. Liver is the main site for drug metabolism, but the intestinal wall, lungs and kidneys are other sites for drug metabolism. Two phases of drug metabolism exists, phase-I and phase-II. Phase-I reactions involve oxidation, reduction and hydrolysis catalyzed by mixed

function oxidase enzymes known as cytochrome P-450 class. These are present in the smooth endoplasmic reticulum of hepatocytes. Phase-II reactions involves conjugation with substance like glucuronic acid and glucuronyl transferase for converting drugs or phase-I metabolites into inactive compounds, facilitating their elimination from the body.[31]

The cytochrome P-450 class is further divided into families, sub-families and allelic forms. Although around 50 enzymes are present in this class, only 6 are responsible for 90-95% of drug metabolism. These are CYP1A2, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5. Most of the clinically significant interactions occurs due to the 3A4 and 2D6 subfamilies. Drugs either induce or inhibit the metabolism of other drugs causing a drug-drug interaction.[31]

Inhibitors are drugs which inhibit the metabolism of substrate drugs by inhibiting the specific enzyme, resulting in accumulation of the substrate drug and toxicity. Clinically important drug interactions due to inhibition of drug metabolism include warfarin metabolism inhibition by phenylbutazone and other drugs like metronidazole, chloramphenicol and cimetidine. Theophylline metabolism is inhibited by macrolide and quinolone antibiotics. Isoniazid inhibits the metabolism of phenytoin resulting in increased phenytoin therapeutic levels and toxicity. Different doses of drugs may be required to inhibit different enzymes. For example at 100mg/day dose, fluconazole inhibits CYP2C9, while at 400mg/day dose it inhibits CYP3A4. Enzyme inhibition of prodrugs has a profound effect, as these have to be converted to active forms by enzyme action, inhibition results in reduced activity. CYP2D6 is required by codeine to convert to morphine to exhibit its analgesic effect, inhibition of this enzyme results in decreased therapeutic effect of codeine.[31]

Inducers increase the metabolism of drugs by stimulating the production of enzymes, increasing the metabolism and excretion of the substrate drug. This decreases the therapeutic effectiveness of the substrate drug. However, this may not be true for drugs whose metabolites are active after biotransformation. Enzyme induction is usually a slow process taking up to a week depending on the half-life of the drug and synthesis of the enzyme, but in case of rifampicin it occurs within 24 hours due to its short half-life. Quinidine metabolism is increased when administered with phenytoin due to the induction of CYP3A4 resulting in decreased concentrations of quinidine by about 60%.[44] Rifampin and carbamazepine may result in decreased concentrations of antiretroviral agent ritonavir due to induction of CYP3A4.[45,46] The use of artemether/lumefantrine combination is contraindicated with dexamethasone as it induces the CYP3A4 metabolism of artemether/lumefantrine and diminishes their antimalarial effect.[31]

Table 1.1 Cytochrome P450 enzyme system substrates, inhibitors and inducers

SUBSTRATE					
CYP1A2	**CYP2C19**	**CYP2C9**	**CYP2D6**	**CYP2E1**	**CYP3A4**
Amitriptyline Caffeine Clomipramine Clozapine Cyclobenzaprine Desipramine Diazepam Haloperidol Imipramine Olanzapine Propranolol R-warfarin Tacrine Theophylline Zileuton	Clomipramine Cyclophosphamide Diazepam Imipramine Lansoprazole Omeprazole Phenytoin Progesterone Propranolol Topiramate	Celecoxib Diclofenac Flurbiprofen Glipizide Ibuprofen Irbesartan Losartan Naproxen Phenytoin Piroxicam Rofecoxib S-warfarin Tamoxifen Torsemide Valdecoxib	Amitriptyline Amphetamines Aripiprazole Clomipramine Clozapine Codeine Tramadol Desipramine Dextromethorphan Fluoxetine Haloperidol Hydrocodone Imipramine Metoprolol Nortriptyline Paroxetine Propranolol Risperidone Tamoxifen Timolol Venlafaxine	Acetaminophen Ethanol Enflurane Halothane Isoflurane	Alprazolam Aripiprazole Amitriptyline Calcium channel blockers Carbamazepine Cisapride Dexamethasone Erythromycin Glyburide Haloperidol HIV protease inhibitors HMG-CoA reductase inhibitors Imipramine Ketoconazole Midazolam Prednisone Quinidine Risperidone Tacrolimus Zolpidem
INHIBITORS					
CYP1A2	**CYP2C19**	**CYP2C9**	**CYP2D6**	**CYP2E1**	**CYP3A4**
Cimetidine Ciprofloxacin Clarithromycin	Cimetidine Fluoxetine Lansoprazole Omeprazole Ritonavir	Amiodarone Chloramphenicol Cimetidine Divalproex	Amitriptyline Cimetidine Clomipramine Fluoxetine	Disulfiram Isoniazid	Amiodarone Azole antifungals

Enoxacin Erythromycin Grapefruit juice Isoniazid Ketoconazole Levofloxacin Norfloxacin Ofloxacin Paroxetine	Sertraline Topiramate	Fluconazole Fluoxetine Itraconazole Ketoconazole Omeprazole Ritonavir Sertraline	Haloperidol Nefazodone Paroxetine Quinidine Ritonavir Sertraline Venlafaxine		Cannabinoids Cimetidine Ciprofloxacin Diltiazem Fluoxetine Grapefruit juice HIV protease inhibitors Macrolide antibiotics (except azithromycin) Methadone Norfloxacin
INDUCERS					
CYP1A2	**CYP2C19**	**CYP2C9**	**CYP2D6**	**CYP2E1**	**CYP3A4**
Carbamazepine Insulin Omeprazole Phenobarbital Phenytoin Rifampin Ritonavir Tobacco	Carbamazepine Phenytoin Rifampin	Phenobarbital Phenytoin Rifampin	Carbamazepine Dexamethasone Phenobarbital Phenytoin Rifampin Ritonavir	Isoniazid Retinoids Tobacco	Barbiturates Carbamazepine Dexamethasone Ethosuximide Phenobarbital Phenytoin Prednisone Rifabutin Rifampin Ritonavir St. john's wort Troglitazone

1.6.1.4 Elimination

Drugs are eliminated through kidney and bile but few clinically important drug-drug interactions are caused due to this mechanism. Thus kidney remains the major source of drug elimination. Major mechanisms involved include active transport/secretion, changes in glomerular filtration or change in urinary pH.[31]

Many drugs are excreted by active secretion into the renal tubules, altering their response. Drugs interact at the active transport sites and inhibit the renal excretion of other drugs. For example penicillins like amoxicillin and probenecid compete for excretion by altering the active transport sites resulting in the excretion of probenecid and retention and reabsorption of amoxicillin.[47] Interactions occur at active transport sites between digoxin and quinidine, verapamil and amiodarone resulting in digoxin toxicity. Similarly, cimetidine inhibits the secretion of procainamide resulting in its toxicity.[48]

Drugs having narrow therapeutic index may be effected by increase or decrease of glomerular filtration rate because of the changes in renal blood flow. For example the steady state concentrations of digoxin, phenytoin and warfarin may decrease when renal clearance increases and vice versa.[48]

Changes in urine pH may change the ionization of weak acidic and basic drugs, thereby altering their reabsorption into the blood. The excretion of weakly acidic drugs like salicylates can be enhanced by increasing the urine pH with alkalinizing agents like antacids, while the excretion of weakly basic drugs like amphetamine can be enhanced by acidifying the urine. This interaction is helpful in treating salicylate and

amphetamine poisoning. Phenobarbitone plasma levels may also be increased with the use of ascorbic acid or other acidifying drugs.[49]

1.6.2 Pharmacodynamics drug-drug interactions

Pharmacodynamic interactions occur when the clinical effect of one drug is altered by the presence of another. The resulting interaction may have a synergistic or antagonistic effect at the receptor site and may be at a cellular, physiological or physiochemical level. Following are the mechanisms involved in pharmacodynamics drug-drug interactions.

1.6.2.1 Synergism

When drugs with similar pharmacological action or active ingredients are simultaneously administered, a synergistic or additive effect is observed. The receptor sites for both the drugs may or may not be same. An example would be the increased risk of bleeding by the concomitant use of aspirin or other NSAIDs with clopidogrel. Risk of cardiac arrhythmias may be increased by the simultaneous use of theophylline and beta agonists such as albuterol. Hypokalemia and digoxin toxicity may occur when amphotericin B is administered concomitantly with digoxin. Some synergistic interactions are beneficial and used clinically, for example insulin is combined with oral hypoglycemic agents for better blood glucose level control, and combination of certain antibiotics are used to combat complex infections.[50]

1.6.2.2 Antagonism

When drugs with opposing pharmacological action are administered simultaneously, an antagonistic effect is observed. These can also be used beneficially, like the antagonistic action of flumazenil is used in case of benzodiazepine overdose or toxicity, naloxone is used for opioid toxicity. In other cases antagonistic drug interactions may

prove harmful, for example cyclo-oxygenase 2 (COX-2) inhibitors inhibits the hypotensive action of beta blockers, diuretics and ACE inhibitors. Another example of antagonist drug-drug interaction is the use of beta-agonists like albuterol with non-selective beta-blockers like propranolol.[50]

1.7 Pharmacoepidemiology

Prevalence of potential drug-drug interactions has been studied throughout the world with varied reports, particularly due to the change in the health care provision system. Developed countries with well-established health care provision and monitoring systems have reports of lesser prevalence of potential drug-drug interactions as compared to the developing countries where the health care provision and monitoring system is not well developed.

1.7.1 Prevalence of potential drug-drug interactions at hospitals

Studies have been conducted to identify the prevalence of potential drug-drug interactions in hospitals at different levels and settings, whether in out-patients or patients admitted to the hospital.

A study in Sweden reported the presence of at least on potential drug-drug interaction in 31% patients in out-patient setting, while only 3% of these interactions were of major clinical significance and 23% were of moderate significance.[51] An American out-patient study reported 82% prescriptions had potential drug-drug interactions when prescribed 5 or more medications.[52] Another study conducted in elderly population of Mexico reported a prevalence of potential drug-drug interactions to be 80%.[53] Study conducted in the university hospital of Thailand reported a prevalence of 27.9% in out-patient setting and 57.8% in the psychiatric department.[54] The prevalence of potential drug-drug interactions was reported to be 25.6% in the outpatients of a medical center

at Taiwan. Severity of 55.7% of these interactions was moderate.[55] A Nepalese study conducted in diabetic outpatients reported a prevalence of potential drug-drug interactions in 52.2% patients. This study also reported the severity of maximum interactions (92.1 %) to be of moderate type.[56]

A Canadian study in the emergency department of a hospital reported an occurrence of potential drug-drug interaction in 31% of the patients.[57] Similarly, an American study conducted in the emergency department reported the presence of potential drug-drug interactions in 47% patients. The risk of potential drug-drug interactions rose with increase in prescribed drugs, 13% patients had a potential drug-drug interaction when they were prescribed 2 drugs while the prevalence increased to 82% when prescribed 7 or more drugs.[58]

Various reports of potential drug-drug interactions in hospital setting exist in literature. A study in Italy reported that 11% patients had at least one potential drug-drug interactions.[59] Analysis of prescriptions in a Dutch university hospital revealed 27.8% patients had at least one potential drug-drug interaction, maximum interactions were reported in nephrology department while least interactions occurred in pediatric surgery.[60] Similarly, a study in Canada also reported a low prevalence of potential drug-drug interactions. Only 19.3% admissions had at least one potential drug-drug interaction.[61] A higher prevalence was reported in patients receiving palliative care in a hospital in UK. Potential drug-drug interactions were reported in 90% of the patients of which 62% were of major severity.[62] A Brazilian study reported the frequency of potential drug-drug interactions to be 49.7% in a teaching hospital. Cardiology and ophthalmology were the departments reported having maximum interactions.[63] In Nepal, a study reported the presence of a potential drug-drug interactions in 21.3% patients.[64] Similarly, an Iranian study also reported an incidence of 20.3% potential

drug-drug interactions in their hospital patients.[65] A study conducted in the pediatric population of Pakistan to assess potential drug-drug interactions reported a prevalence of 66.9%,[66] while another study reported the prevalence to be 25.8%.[67]

1.7.2 Prevalence of potential drug-drug interactions at critical care units

Drug therapy in the critical care units poses a challenge different to that of the general wards in the hospital. Complex physiological and pathological conditions of the patients require administration of multiple drugs targeted to achieve better therapeutic results, but this polypharmacy increases the likelihood of potential drug-drug interactions. Further complications like adverse drug reactions and drug resistance also results of polypharmacy.[68,69] It has been reported that nearly 5% of all adverse drug reactions are due to potential drug-drug interactions.[70,71,72]

Frequency of potential drug-drug interactions was reported to be 8.1% in prescriptions of a medical intensive care unit of a tertiary care hospital in Netherland.[73] A study in Brazil reported the presence of at least one potential drug-drug interactions in 55% of ICU patients while 22% prescriptions were reported to have potential drug-drug interactions.[74] An Indian study conducted in the medical intensive care unit reported a high prevalence of potential drug-drug interactions, 90.02% patients presented with a potential drug-drug interactions.[75] A study reported pharmacokinetic interactions to be present in 72% prescriptions of an ICU in Iran.[76]

An American study reported prevalence of potential drug-drug interactions to be 7.3% in patients admitted to the surgical intensive care unit.[77] A retrospective Brazilian study conducted to quantitatively evaluate the use of medications reported a total of 61.15% drug-drug interactions, with 33.92% and 27.23% being severe and moderate in nature

respectively.[69] A study conducted in ICU's of Netherland using Dutch national drug database reported 40.3% prescriptions having a potential drug-drug interaction.[60]

Cardiac intensive care units report a higher incidence of potential drug-drug interactions. An American study conducted in the cardiac and cardiothoracic intensive care unit reported potential drug-drug interactions to be present in 56.25% prescriptions.[9] Another American study reported that 37% patients admitted to the cardiac intensive care unit experienced QT prolongation due to drug-drug interactions.[78]

1.8 Levels and clinical significance of PDDIs

Drug interactions are categorized into various levels to help decide whether an interaction poses a serious implication on the health of the patient or not. Drug interactions can be classified into the following levels. [79]

Table 1.2 Levels of potential drug-drug interactions

Level	Sub classification	Outcome
Severity of PDDI	Contraindicated	Drug combination is contraindicated for simultaneous use
	Major	Drug combination may have a life threating effect and requires intervention to prevent serious effects
	Moderate	Drug combination may worsen the patients condition and require change in therapy
	Fair	Drug combination may increase the severity or frequency of an adverse effect but has no effect on the therapeutic effect of the drugs
Documentation of PDDI	Excellent	Documentation of the drug interaction is reported in controlled studies
	Good	Documentation in well controlled studies is lacking but the interaction is strongly suggested in some studies
	Fair	Documentation is poor but interaction can be suspected on the basis of pharmacological considerations, like existence of an interaction for a similar drug.
Onset of PDDI	Rapid	The interaction shows its effect within 24 hours
	Delayed	The interaction shows its effect after 24 hours, may be days or even weeks

Clinical significance	1	Drug interaction is of contraindicated severity
	1	Drug interaction is of major severity and excellent or good documentation
	2	Drug interaction is of moderate severity and excellent or good documentation
	3	Drug interaction is of minor severity and excellent or good documentation
	4	Drug interaction is of major or moderate severity and fair documentation
	5	Drug interaction is of minor severity and fair documentation
	5	Drug interaction is of major or moderate or minor severity and unknown documentation

1.9 Factors affecting PDDIs

Potential drug-drug interactions (PDDIs) are affected by many factors like number of prescribed drugs to the patient, duration of stay in the unit, age and gender of the patient. Many studies reported a positive relationship between the increasing number of prescribed drugs and PDDIs. A study conducted in Saudi Arabia reported a significant association between number of prescribed drugs and PDDIs.[80] In another study effect of associated factors on PDDIs in cardiac patients also reported a significant relationship between number of prescribed drugs and PDDIs.[81] A retrospective study conducted in a Brazilian hospital revealed that patients prescribed with five or more drugs had an odd of PDDIs seven times higher than other patients.[82] The extent to which polypharmacy is associated with PDDIs was studied in Taiwan also reported a positive

significant association between number of prescribed drugs and PDDIs.[55] A Mexican study conducted in elderly ambulatory population also reported a significant association between PDDIs and polypharmacy.[53]

Similarly, age of the patient is another factor affecting PDDIs. A significant association ($P < 0.0001$) between age and PDDIs was reported in a study.[83] However, a Swedish study reported that the number of PDDIs decrease with increasing age.[84] A Brazilian study also reported similar results with age having no significant effect on the number of PDDIs.[74] However, a study conducted in a Brazilian teaching hospital reported a positive correlation between age and number of PDDIs.[63]

The association of gender with the number of PDDIs can be significant as well as insignificant as reported by various study. Gender was not found to be a significant factor affecting the number of PDDIs in one study. A nine month cross sectional study reported this insignificant association.[83] Another study reported a similar result.[85] While an Italian outpatient study reported that male patients were more prone to PDDIs as compared to females.[59]

Duration of stay in the hospital or the hospital unit also has an effect on the number of PDDIs. A significant association was found between the duration of stay in hospital and number of PDDIs in a four months prospective study in Nepal.[64] A study in Brazil reported odds ratio, (OR= 1.81; 95% CI = 1.29-2.74; $P<0.004$), Significant association between duration of hospital stay and number of PDDIs.[82] Other studies have also reported a similar association between length of hospitalization and number of PDDIs.[81,74] Other factors affecting the number of potential drug-drug interactions include disease, co-morbidities, multiple prescribers, education level of the patient and various health care settings.[83,85,86,87]

1.10 Medication errors and their significance

In medical practice medication errors are common due to the complex medical management and human nature. Modern day physicians frequently commit medication errors, the nature of some are less severe while some may also cause death. Medication errors are one of the common causes for adverse drug reactions and events. It includes prescribing and administration errors. Error in dose or strength of the drug, route, omission and incomplete information are common prescribing errors while administration errors include wrong time or dose, omitted or extra dose and unauthorized or wrong drug.[88,89] A study conducted in 36 health care facilities of United States of America (USA) reported 19% errors in dose, of which wrong administration time contributed to 43% of the errors, omission errors were 30%, wrong dose errors were 17% and unauthorized drug errors were 4%.[90] While another study reported prescribing errors to be 6.24%. Of these 30.8% were considered clinically significant. This study also showed that of all the prescribing errors 64.4% could be prevented by implementing computerized prescriber order entry.[91] Medication errors were reported to be 14.7% in a study conducted in United Kingdom (UK).[92] In pediatrics, medication errors were reported to be 7.3% and 11.4%. The frequency of medication errors is similar for children and adults but the potential harm due to these errors in children is far greater than adults.[89] Medication errors thus are common and equally important to consider as the likelihood of patient benefitting from therapy reduces whenever a medication error is encountered.

1.11 Rationale to conduct present study

Pakistan has one of the lowest health indicators mainly because of the low percentage of GDP allocated to the health sector. Only 2% is spent on the health compared to 5-14% spent in developed countries.

Pakistan is a country which lacks definitive health care structure. Although tertiary hospitals are present but the lack of proper drug monitoring and reporting systems make it vulnerable to drug related problems. To make matters worse, awareness about this deficient system is also lacking among people as well as the health professionals. Drugs are overused due to various marketing tactics and physicians are overburdened, making them vulnerable to errors in drug prescription.[93]

Pharmacoepidemiological studies must be carried out to identify the scope and extent of the problem but studies are lacking in this area. The current study is carried out in the critical care units of tertiary care hospitals as critical care poses a unique challenge because of the complex physiological condition, co-morbidities and critical condition of the patient. Although some studies have been carried out to report the drug use and related problems in general hospital wards but no study has been reported in the critical care unit. This will be the first definitive study carried out in critical care setting in Pakistan. This study will provide statistical data for the identification of the scope and extent of the drug related problems on the basis of which recommendations can be made for health care professionals and prescribers ultimately improving the health care system of our country.

1.12 Aim and Objectives

The aim and objectives of the study are to;

1. Identify the prevalence of potential drug-drug interactions in the patients admitted to the critical units at tertiary care hospitals.
2. Study the drug prescribing patterns in the critical care units with special reference to discrepancies in dose in specific indications.
3. Determine the role and significance of various parameters like number of prescribed drugs, length of stay and age on the number of potential drug-drug interactions.
4. Provide data for clinical interventions of frequently occurring and potentially harmful drug-drug interactions in various critical care units.
5. Provide management guidelines for specific drugs reported for maximum medication errors in the critical care units.

Chapter 2:

Methodology

2 METHODOLOGY

2.1 Research design and setting

This prospective cross-sectional study was conducted at critical care units of the following tertiary care hospitals in Peshawar:

- Lady Reading Hospital (LRH), Peshawar
- Khyber Teaching Hospital (KTH), Peshawar
- Hayatabad Medical Complex (HMC), Peshawar
- Northwest General Hospital and Research Center (NWGH & RC), Peshawar

LRH, KTH and HMC are Government tertiary care hospitals, functioning under the Government of Khyber Pakhtunkhwa, while NWGH & RC is a private tertiary care hospital.

The critical care units included in this study were:

- Surgical Intensive Care Unit (SICU)
- Medical Intensive Care Unit (MICU)
- Cardiac Intensive Care Unit (CCU)
- Stroke Unit (SU)

SICU, MICU and CCU were present in all the four hospitals, while SU was only present in NWGH.

2.2 Sample Size

Sample size was calculated using the following formula for known populations.[94]

$$n' = \frac{N Z^2 P (1-P)}{d^2 (N-1) + Z^2 P (1-P)}$$

Where,

n' = sample size with finite population correction

N = Population size

Z = Z statistic for level of confidence

P = Expected proportion

d = precision

In the above mentioned formula, the anticipated prevalence was considered as 50% (P = 0.5); 5% margin of error was considered (d = 0.05); and 95% confidence level (Z = 1.96) was used.

The above mentioned formula was used to calculate sample size of each unit of each hospital using the known population, i.e. number of patients admitted to each unit per year. (Table 2.1) A total sample size of 2960 patients was collected during the study period (July 2012 – July 2013).

Table 2.1 Populations and respective samples taken

		LRH	***KTH***	***HMC***	***NWGH & RC***
SICU	Population	431	454	438	540
	Sample Taken	210	210	210	230
MICU	Population	421	430	418	196
	Sample Taken	210	210	210	200
CCU	Population	800	760	785	700
	Sample Taken	260	260	260	250
SU	Population	-	-	-	600
	Sample Taken	-	-	-	240

2.3 Data Collection

Cluster sampling technique was employed to collect patient data from critical care units. Sample were randomly collected and the medication charts of the patients were accessed with due approval from ethical committees of the hospitals. Demographics and medication profile was collected on a predesigned proforma.

2.4 Proforma Design

The designed proforma for data collection comprised of two parts.

1. Patient demographics: This included name, admission number, age and gender of the patient, date of admission to the critical care unit and date of discharge and diagnosis of the patient.
2. Patient medication profile: This included the names and the number of the drugs prescribed to the patient along with the indications, and the dosage regimen and duration of therapy.

2.5 Exclusion criteria

Following exclusion criteria was used in this study:

- Patient prescribed less than 2 drugs.
- Topical and herbal preparations, multivitamins, IV stock solutions and STAT drugs.

2.6 Inclusion criteria

Patients admitted only in the critical care units having at least 24 hours stay in the unit were include in the study.

2.7 Study approval

This research study was approved by the respective Ethical Committees of the four tertiary care hospitals included in the study. Authorization to access patient medication charts was granted by the respective hospital committees. Names of the patients, their identification numbers and medical records were kept confidential. Good clinical practice (GCP) guidelines were followed under the declaration of Helsinki (1964) by the International Conference on Harmonization and Nuremburg Code.[95]

2.8 Data Evaluation

The medication profiles of patients were evaluated for drug-drug interactions using Micromedex Drug-Reax (Klasco RK (Ed): DRUG-REAX® System. Thomson Micromedex, Greenwood Village, Colorado) and Drug interaction facts, while the dose related parameters were evaluated using Micromedex Drug-Dex (Klasco RK (Ed): DRUGDEX® System. Thomson Micromedex, Greenwood Village, Colorado).

2.9 Case definition & Variables

The Micromedex Drug-Reax system categories severity, documentation, onset, nature and mechanisms of PDDIs.

The definitions of the various categories as described by Micromedex Drug-Reax are as follows.

2.9.1 Severity

Contraindicated: The drugs are contraindicated for concurrent use.

Major: The interaction may be life threatening and to prevent the risk of serious adverse effects, medical intervention may be required.

Moderate: The interaction may exacerbate the patient's medical condition, requiring a change in therapy.

Minor: The interaction will have limited clinical effects and may only cause an increase in the severity or frequency of an adverse effect, not requiring any major change in therapy.

Unknown: The severity of the interaction is not available.

2.9.2 Onset

Rapid: The resultant effect of the interaction occurs within 24 hours of the administration of the interacting drug pair.

Delayed: The resultant effect of the interaction occurs after 24 hours of the administration of the interacting drug pair, maybe even weeks or months.

Unknown: The onset of the interaction is not available.

2.9.3 Documentation

Excellent: The existence of the interaction is clearly established in controlled studies.

Good: The existence of the interaction is strongly suggested in literature but well controlled studies are limited.

Fair: Literature available is poor but clinicians suspect the presence of interactions due to pharmacological considerations, or an interaction for a similar drug is well documented in literature.

Unknown: The scientific evidence for the interaction is not available.

2.9.4 Nature of interaction

Pharmacokinetic: Interaction occurs due to changes in absorption, distribution, metabolism or elimination of a drug due to the presence of another drug.

Pharmacodynamics: Interaction occurs due to additive or antagonistic effect of a drug on another.

Unknown: Nature of the interaction is not known.

2.9.5 Mechanism of interaction

Absorption: Drug interaction occurs at the level of absorption affected by the presence of another drug.

Distribution: One drug effects the distribution of another drug in the physiological fluids of the body.

Metabolism: Simultaneous administration of 2 drugs may enhance or inhibit their metabolism in the body.

Elimination: One drug affects the elimination of another drug from the body.

Synergism: Excessive response due to the simultaneous administration of drugs with similar pharmacological response.

Antagonism: Reduced effects due to the concomitant administration of drugs having opposing pharmacological effects.

Unknown: The mechanism of interaction is not known.

Drug Interaction Facts classifies PDDIs on a scale of 1 to 5, with 1 being the most severe and 5 being the least severe interaction.

2.10 Prevalence of PDDIs

The prevalence of PDDIs was calculated as follows:

$$\boldsymbol{prevalence\ of\ PDDIs} = \frac{\boldsymbol{total\ number\ of\ patients\ having\ PDDIs}}{\boldsymbol{total\ number\ of\ patients}}$$

2.11 Clinically important PDDIs

Following PDDIs were considered as clinically important:

- PDDIs having Severity of contraindicated
- PDDIs having severity of major and of excellent or good documentation
- PDDIs having severity of moderate and of excellent or good documentation

On this basis, PDDIs having severity of major and of excellent or good documentation were considered of having clinical significance 1, and PDDIs having severity of moderate and of excellent or good documentation were considered of having clinical significance 2. The rest of the interactions were considered to be of lesser clinical significance.

2.12 Medication Errors

The medications for which deviations in doses were present, categorized as subtherapeutic and overdose. Doses or frequency prescribed less than the recommended doses as per Micromedex DrugDex were considered as subtherapeutic dose while doses or frequency greater than the recommended dose were considered as overdose.

2.13 Statistical analysis

Descriptive statistics were used to present the data variables such as gender, age, number of prescribed drugs, duration of stay, number of interaction per patient and number of interactions per unit. Mean, median and ranges were applied where it was necessary to describe the results. Patient age, gender, duration of stay and number of prescribed drugs were considered as predictors for potential drug interactions. Logistic regression was used to determine the effect of these predictors on exposure to potential

drug-drug interactions. Odds ratio for the predictors of PDDI were also be computed by using logistic regression. Potential drug-drug interactions was the dependent variable in the model (present = 1 and absent = 0) while predictors were the independent variables. In order to check the relationship between predictors and PDDI, multivariate analysis was performed. The variables were entered in binary form and labelled as 0 and 1. P-value of 0.05 or less was considered as statistically significant. One way ANOVA was used to compare the means of PDDIs between the four hospitals. For statistical analysis of data IBM SPSS Statistics for Windows, Version 20 (Armonk, NY: IBM Corp.) was used.

Chapter 3:

Results & Discussion

3 RESULTS AND DISCUSSION

3.1 SURGICAL INTENSIVE CARE UNIT (SICU)

3.1.1 Lady Reading Hospital

3.1.1.1 General Patient Characteristics

A total of 210 patients were analyzed in the SICU of LRH, of which 102 (48.6%) were males and 108 (51.4%) were females. The patients mean age was 34.25 while the range was 0.3 to 75 years. Of the total patients, 70.5% were between the ages of 19 to 59 years, 16.6% were of 18 years and below, while 12.9% patients were of 60 years and above. Mean duration of stay in the critical care unit was 4.15 ± (2.18) days and the mean number of prescribed drugs were 5 ± (1.42) as shown in Table 3.1.

The top three leading causes of admission in the SICU of LRH were brain tumor, road traffic accident cases (RTA) and exploratory laparotomy as shown in Figure 3.1.

Table 3.1 General Patient Characteristics in SICU of LRH

Variables	**Frequency (%)**
Gender	
Male	102 (48.6%)
Female	108 (51.4%)
Age (years)	
Mean ± SD	34.25 (± 16.52)
Median	33.5
Range	0.3-75
≤ 18	35 (16.6%)
19-59	148 (70.5%)
≥ 60	27 (12.9%)
Drugs prescribed per patient	
Mean ± SD	5 ± (1.42)
Median	5
Range	2-9
≤ 4	86 (41%)
5-6	96 (45.7%)
≥ 7	28 (13.3%)
Stay in ICU (days)	
Mean ± SD	4.15 ± (2.18)
Median	4
Range	1-21
≤ 2	45 (21.4%)
3-5	121 (57.6%)
≥ 6	44 (21%)

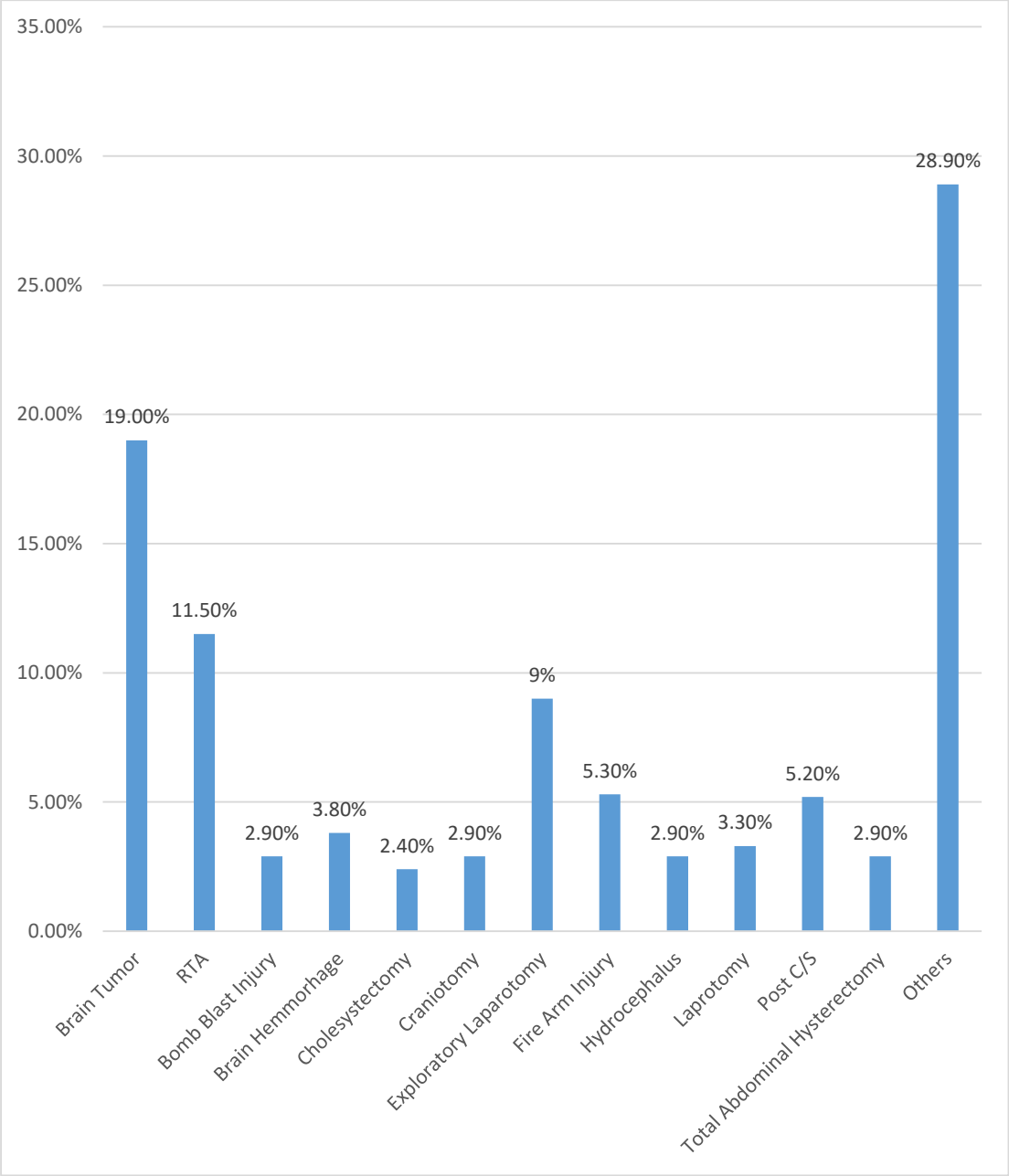

Figure 3.1 Causes of Admission to SICU of LRH

3.1.1.2 Prevalence of Potential drug-drug interactions

A prevalence of 28.6% PDDIs was reported in the patients of SICU of LRH. Forty seven patients had one PDDI, four patients had two PDDIs, eight patients had three PDDIs and one patient had five PDDIs as shown in Table 3.2.

Table 3.2 Prevalence of PDDIs in SICU of LRH

No. Of PDDIs	Frequency	Percentage %
1	47	22.4
2	4	1.9
3	8	3.8
5	1	0.5

3.1.1.3 Categories of PDDIs

The PDDIs reported in the SICU of LRH were classified on the basis of severity, documentation and onset. The type and mechanisms of interactions were also identified. A total of 22 interacting drug pairs were identified which caused 84 potential drug-drug interactions. The severity of 76.2% PDDIs were major, 21.4% were moderate while 2.4% were of minor severity. Documentation of 67.8% PDDIs were fair, 27.4% of the PDDIs were of good and 4.8% of the PDDIs were of excellent documentation. On the basis of onset of PDDIs, 76.2% were of unknown onset, 1.2% PDDIs were of rapid and 22.6% were of delayed onset. Pharmacokinetic interactions were present in 27.4% PDDIs and pharmacodynamics interactions were present in 25% PDDIs while 47.6% PDDIs were of unknown type. In terms of mechanism, synergism and metabolism were involved in 25% PDDIs each, absorption and elimination contributed to 1.2% PDDIs each, while 47.6% PDDIs were of unknown mechanisms as shown in Table 3.3.

Table 3.3 Categories of PDDIs in SICU of LRH

Variable	**Frequency (%)**
Severity of PDDIs	
Major	64 (76.2%)
Moderate	18 (21.4%)
Minor	2 (2.4%)
Documentation of PDDIs	
Excellent	4 (4.8%)
Good	23 (27.4%)
Fair	57 (67.8%)
Onset of PDDIs	
Rapid	1 (1.2%)
Delayed	19 (22.6%)
Unkonwn	64 (76.2%)
Type of Interaction	
Pharmacodynamic	21 (25%)
Pharmacokinetic	23 (27.4%)
Unknown	40 (47.6%)
Mechanism of Interaction	
Synergism	21 (25%)
Absorption	1 (1.2%)
Metabolism	21 (25%)
Elimination	1 (1.2%)
Unknown	40 (47.6%)

3.1.1.4 Interacting Drug Pairs

In the SICU of LRH, 22 interacting drug pairs were identified causing 84 drug-drug interactions, of these interacting drug pairs, 5 were involved in 63 (74.9%) interactions of which 4 were major and 1 was moderate as shown in Table 3.4.

Table 3.4 Interacting drug pairs in SICU of LRH

Interacting pair	Frequency	Percentage %
ketorolac-valproate sodium	34	40.5%
nimodipine-valproate	9	10.7%
dexamethasone-nimodipine	7	8.3%
tramadol-valproate sodium	7	8.3%
enoxaparin-ketorolac	6	7.1%
clarithromycin-valproate	3	3.6%
ketorolac-nimodipine	3	3.6%
ketorolac-phenytoin	1	1.2%
dexamethasone-phenytoin	1	1.2%
aspirin-clopidogrel	1	1.2%
aspirin-ranitidine	1	1.2%
aspirin-enoxaparin	1	1.2%
clarithromycin-tramadol	1	1.2%
clopidogrel-enoxaparin	1	1.2%
meropenem-valproate	1	1.2%
imipenem-valproate sodium	1	1.2%

clarithromycin-nifedipine	1	1.2%
diclofenac-metronidazole	1	1.2%
clarithromycin-levofloxacin	1	1.2%
linezolid-tramadol	1	1.2%
aspirin-dexamethasone	1	1.2%
phenytoin-ranitidine	1	1.2%

3.1.1.5 Clinically significant PDDIs in the SICU of LRH

Analysis of the drug interacting pairs for clinical significance yielded 9 pairs having a clinical significance of 1 and 2. These pairs contributed to 29.7% of the total PDDIs (25 of 84), 5 of which were of clinical significance 1 while 4 were of clinical significance 2. The clinically significant drug interacting pairs along with their potential outcomes are shown in Table 3.5.

Table 3.5 Clinically important interacting pairs and their potential outcomes in SICU of LRH

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Meropenem-valproate	1	1	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	96,97,98,99
Enoxaparin-ketorolac	1	1	Increased risk of bleeding.	100,101,102,103
Imipenem-valproate	1	6	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	104
Linezolid-tramadol	1	1	Increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental status changes)	105,106
Aspirin-enoxaparin	1	1	Increased risk of bleeding.	100,101,102,103
Nimodipine-valproate	2	9	Nimodipine toxicity (dizziness, headache, flushing, peripheral edema).	107
Dexamethasone-phenytoin	2	1	Decreased dexamethasone effectiveness.	108,109,110,111
Ketorolac-nimodipine	2	3	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	112,113
Aspirin-dexamethasone	2	1	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	114,115

3.1.1.6 Association of PDDIs with contributing factors in SICU at LRH

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

A significant association was found between the presence of PDDIs with the patients prescribed 5 or more drugs (OR = 73.59; 95%CI = 9.882-548.004; p = 0.000). An insignificant association was found between the presence of PDDIs and duration of stay of 4 or more days (OR = 1.308; 95%CI = 0.634-2.701; p = 0.467), and with gender (OR = 1.034; 95%CI = 0.515-2.075; p = 0.926). The results are shown in Table 3.6.

Table 3.6 logistic regression analysis of SICU in LRH

Variable	**Patients (n)**		**OR (95%CI)**	**p-value**
	Interactions present (n=60)	**Interactions absent (n=150)**		
Prescribed drugs				
< 5	1	85		
≥ 5	59	65	73.59 (9.882-548.004)	0.000
Duration of stay				
< 4	20	75		
≥ 4	40	75	1.308 (0.634-2.701)	0.467
Gender				
Male	31	71		
Female	29	79	1.034 (0.515-2.075)	0.926

3.1.1.7 Drugs used

A total of 63 drugs were prescribed in the SICU of LRH appearing 1049 times in all the medication charts as shown in Table 3.7.

Table 3.7 Frequencies of commonly used drugs in SICU of LRH

Drug Name	Dosage Form	Frequency
Metronidazole	Intravenous	115
Omeprazole	Intravenous	108
Ceftriaxone	Intravenous	103
Ranitidine	Intravenous	81
Dimenhydrinate	Intravenous	80
Piperacillin+Tazobactam	Intravenous	75
Dexamethasone	Intravenous	72
Ketorolac	Intravenous	71
Valproate Sodium	Intravenous	57
Albuterol	Nebules	41
Enoxaparin	Subcutaneous	40
Tramadol	Intravenous	34
Cefoperazone+Sulbactam	Intravenous	16
Meropenem	Intravenous	14
Nimodipine	Tablets	11
Ipratropium	Nebules	10
Clarithromycin	Intravenous	9
Imipenem+Cilastatin	Intravenous	8
Amikacin	Intravenous	7
Dopamine	Intravenous	7
Beclomethasone	Nebules	7
Furosemide	Intravenous	6
Benzylpenicillin	Intravenous	4
Tranexamic Acid	Intravenous	4
Heparin	Subcutaneous	4

Calcitriol	Intravenous	4
Vitamin K	Intravenous	4
Ciprofloxacin	Intravenous	3
Esomeprazole	Intravenous	3
Linezolid	Intravenous	3
Vancomycin	Intravenous	3
Lactulose	Syrup	3
Dobutamine	Intravenous	3
Co-Amoxiclav	Intravenous	2
Ceftizoxime	Intravenous	2
Amlodipine	Tablets	2
Ceftazidime	Intravenous	2
Metoclopramide	Intravenous	2
Omeprazole	Tablets	2
Diclofenac Na	Intravenous	2
Gentamicin	Intravenous	2
Paracetamol	Intravenous	2
Clopidogrel+Aspirin	Tablets	1
Phenytoin	Intravenous	1
Nifedipine	Tablets	1
Levetiracetam	Tablets	1
Rifaximin	Tablets	1
Piracetam	Intravenous	1
Atorvastatin	Tablets	1
Paracetamol+Orphenadrine	Tablets	1
Hydrocortisone	Intravenous	1
Ferrous Sulfate+Folic Acid	Tablets	1
Folic Acid	Tablets	1
Octreotide	Subcutaneous	1
Levofloxacin	Intravenous	1
Alfacalcidol	Tablets	1
Domperidone	Tablets	1
Calcium Gluconate	Intravenous	1

Domperidone	Syrup	1
Tizanidine	Tablets	1
Calcium	Tablets	1
Olmesartan+Hydrochlorothiazide	Tablets	1
Doxazosin	Tablets	1

3.1.1.8 Indications

Secondary infection was the most prevalent indication in the SICU of LRH (241 cases of 1049) followed by stress ulcer (193 cases), post-operative infection and pain (100 cases each), emesis (84 cases), asthma (58 cases), seizures (57 cases), cerebral edema (54 cases), deep vein thrombosis (34 cases), while the rest of the cases were contributed by other indications.

3.1.1.9 Drug class

A total of 24 drug classes were used in the SICU of LRH with antibacterial being the most prevalent drug class as shown in Table 3.8.

Table 3.8 Frequencies of Drug classes used at SICU of LRH

Drug Class	Frequency
Antibacterial	367
PPI	113
Analgesic	99
Antiemetic	84
H2 Receptor Antagonist	80
Corticosteroid	80
Anticonvulsant	58
Bronchodilator	51
Anticoagulant	43
Calcium Channel Blocker	12
Nutriceutical	11
Vasopressor	10
Diuretic	6
Hemostatic	4
Laxative	2
Clotting Activator	2
Antiplatelet	1
HMG Co A Reductase Inhibitor	1
ARBs	1
Nootropic Agent	1
Liver Protectant	1
Skeletal Muscle Relaxant	1
Endocrine Metabolic Agent	1
Adrenergic Blocker	1

3.1.1.10 Dosing errors at SICU of LRH

Out of the total 1030 cases, 150 (14.6%) had subtherapeutic doses while 71 (6.9%) had overdoses as shown in Table 3.9 and Table 3.10 respectively.

Table 3.9 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Piperacillin + Tazobactam	Intravenous	72
Ranitidine	Intravenous	44
Nimodipine	Tablets	8
Meropenem	Intravenous	7
Heparin	Subcutaneous	4
Imipenem + Cilastatin	Intravenous	3
Dexamethasone	Intravenous	2
Ceftazidime	Intravenous	2
Paracetamol	Intravenous	2
Gentamicin	Intravenous	1
Dimenhydrinate	Intravenous	1
Ketorolac	Intravenous	1
Hydrocortisone	Intravenous	1
Phenytoin	Intravenous	1
Lactulose	Syrup	1

Table 3.10 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Dexamethasone	Intravenous	48
Ranitidine	Intravenous	8
Enoxaparin	Subcutaneous	5
Omeprazole	Intravenous	2
Beclomethasone	Nebules	2
Dimenhydrinate	Intravenous	1
Meropenem	Intravenous	1
Vancomycin	Intravenous	1
Ipratropium	Nebules	1
Amlodipine	Tablets	1

3.1.2 Khyber Teaching Hospital (KTH)

3.1.2.1 General Patient Characteristics

In the SICU of KTH, 210 patients were analyzed, 149 (71.0%) were males and 61 (29.0%) were females. The mean age of the patients was 34.43 years. Age of the patients ranged from 0.4 to 80 years. A total of 70.5% patients were between the ages of 19 to 59 years, 15.2% were of 18 years and below, and 14.3% patients were of 60 years and above. Mean duration of stay in the critical care unit was 4.05 ± (2.85) days, while the mean number of prescribed drugs were 5.37 ± (1.42) as shown in Table 3.11.

The top three leading causes of admission in the SICU of KTH were brain tumor, road traffic accident cases (RTA) and exploratory laparotomy as shown in Figure 3.2.

Table 3.11 General Patient Characteristics at SICU of KTH

Variables	**Frequency (%)**
Gender	
Male	129 (61.4%)
Female	81 (38.6%)
Age (years)	
Mean ± SD	34.43 (± 18.20)
Median	30
Range	0.4-80
≤ 18	32 (15.2%)
19-59	148 (70.5%)
≥ 60	30 (14.3%)
Drugs prescribed per patient	
Mean ± SD	5.37 ± (1.42)
Median	5
Range	2-9
≤ 4	56 (26.7%)
5-6	117 (55.7%)
≥ 7	37 (17.6%)
Stay in ICU (days)	
Mean ± SD	4.05 ± (2.85)
Median	3
Range	1-19
≤ 2	64 (30.5%)
3-5	81 (38.5%)
≥ 6	65 (31%)

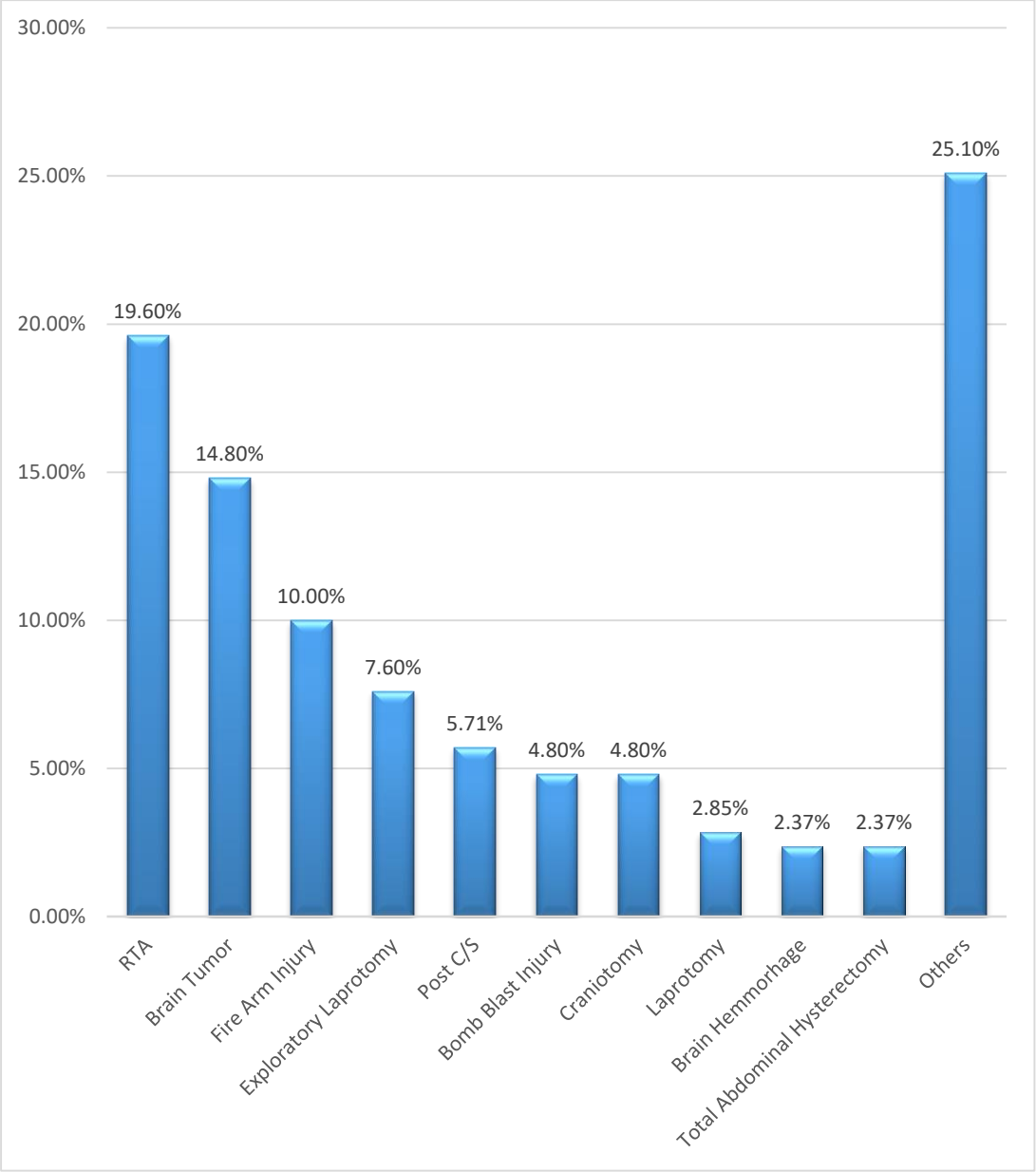

Figure 3.2 Causes of admission to SICU of KTH

3.1.2.2 Prevalence of Potential drug-drug interactions

The prevalence of PDDIs in patients of SICU of KTH was reported to be 35.2%. Fifty nine patients had one PDDI, eight patients had two PDDIs, four patients had three PDDIs and three patients had four PDDIs as shown in Table 3.12.

Table 3.12 Prevalence of PDDIs at SICU of KTH

No. Of PDDIs	Frequency	Percentage %
1	59	28.1
2	8	3.8
3	4	1.9
4	3	1.4

3.1.2.3 Categories of PDDIs

Severity, documentation, onset, type and mechanism of interactions were the parameters used to classify the PDDIs reported in the SICU of KTH. A total of 22 interacting drug pairs were identified resulting in 96 drug-drug interactions. According to severity 72.9% of the PDDIs were major, 22.9% were moderate, while the percentage of minor severity and contraindicated PDDIs was 2.1% each. Fairly documented PDDIs were 68.8%, good documented PDDIs were 23.9% and excellent documented PDDIs were 7.3%. The onset of 66.7% PDDIs was unknown while 5.2% PDDIs were of rapid and 28.1% were of delayed onset. According to type of interactions, 19.8% PDDIs were of pharmacodynamics and pharmacokinetic type each while 60.4% were of unknown type. In terms of mechanism 19.8% PDDIs were due to metabolism, 18.8% were due to synergism, 1.0% were due to antagonism while 60.4% were of unknown mechanisms as shown in Table 3.13.

Table 3.13 Categories of PDDIs at SICU of KTH

Variable	Frequency (%)
Severity of PDDIs	
Major	70 (72.9%)
Moderate	22 (22.9%)
Minor	2 (2.1%)
Contraindicated	2 (2.1%)
Documentation of PDDIs	
Excellent	7 (7.3%)
Good	23 (23.9%)
Fair	66 (68.8%)
Onset of PDDIs	
Rapid	5 (5.2%)
Delayed	27 (28.1%)
Unkonwn	64 (66.7%)
Type of Interaction	
Pharmacodynamic	19 (19.8%)
Pharmacokinetic	19 (19.8%)
Unknown	58 (60.4%)
Mechanism of Interaction	
Synergism	18 (18.8%)
Antagonism	1 (1.0 %)
Metabolism	19 (19.8%)
Unknown	58 (60.4%)

3.1.2.4 Interacting Drug Pairs

In the SICU of KTH, 22 interacting drug pairs were identified resulting in 96 drug-drug interactions, of these interacting drug pairs, 6 were involved in 72 (75.0%) interactions of which 3 were major and 3 were moderate as shown in Table 3.14.

Table 3.14 Interacting drug pairs in SICU of KTH

Interacting pair	Frequency	Percentage %
ketorolac-valproate sodium	41	42.7%
clarithromycin-valproate	10	10.4%
enoxaparin-ketorolac	7	7.3%
nimodipine-valproate	6	6.2%
meropenem-valproate	4	4.2%
ketorolac-nimodipine	4	4.2%
dexamethasone-nimodipine	3	3.1%
clarithromycin-tramadol	3	3.1%
tramadol-valproate sodium	3	3.1%
clarithromycin-nifedipine	2	2.1%
clarithromycin-nimodipine	2	2.1%
ketorolac-phenytoin	1	1.0%
dexamethasone-phenytoin	1	1.0%
imipenem-valproate sodium	1	1.0%
diclofenac-metronidazole	1	1.0%
clarithromycin-levofloxacin	1	1.0%
albuterol-linezolid	1	1.0%

linezolid-tramadol	1	1.0%
Cefoperazone-heparin	1	1.0%
phenytoin-ranitidine	1	1.0%
salmeterol-linezolid	1	1.0%
gentamicin-piperacillin	1	1.0%

3.1.2.5 Clinically significant PDDIs in SICU of KTH

Clinically significant PDDIs were identified using the predetermined criterion and analysis resulted in the identification of 9 interacting pairs which were of clinical significance 1 and 2. These 9 pairs contributed to 29.2% of the total potential drug-drug interactions (28 of 96), of which 6 were of clinically significance 1 while 3 were of clinical significance 2. These clinically significant PDDIs along with their potential outcomes are shown in Table 3.15.

Table 3.15 Clinically important interacting pairs and their potential outcomes in SICU of KTH

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Meropenem-valproate	1	4	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	96,97,98,99
Enoxaparin-ketorolac	1	7	Increased risk of bleeding.	100,101,102,103
Imipenem-valproate	1	1	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	104
Linezolid-tramadol	1	1	Increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental status changes)	105,106
Albuterol-linezolid	1	1	Increase risk of cardiovascular adverse effects.	116,117
Salmeterol-linezolid	1	1	Increase risk of cardiovascular adverse effects.	116,118
Nimodipine-valproate	2	6	Nimodipine toxicity (dizziness, headache, flushing, peripheral edema).	107
Dexamethasone-phenytoin	2	1	Decreased dexamethasone effectiveness.	108,109,110,111
Ketorolac-nimodipine	2	6	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	112,113

3.1.2.6 Association of PDDIs with other parameters in SICU of KTH

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

A significant association was found between the presence of PDDIs with the patients prescribed 5 or more drugs (OR = 17.392; 95%CI = 5.109-59.212; p = 0.000), and with gender (OR = 0.330; 95%CI = 0.168-0.647; p = 0.001). An insignificant association was found between the presence of PDDIs and duration of stay of 3 or more days (OR = 1.762; 95%CI = 0.860-3.609; p = 0.121). The results are shown in Table 3.16.

Table 3.16 logistic regression analysis in the SICU of KTH

Variable	**Patients (n)**		**OR (95%CI)**	**p-value**
	Interactions present (n=74)	**Interactions absent (n=136)**		
Prescribed drugs				
< 5	3	53		
≥ 5	71	83	17.392 (5.109-59.212)	0.000
Duration of stay				
< 3	17	47		
≥ 3	57	89	1.762 (0.860-3.609)	0.121
Gender				
Male	55	74		
Female	19	62	0.330 (0.168-0.647)	0.001

3.1.2.7 Drugs used

A total of 50 drugs were prescribed in the SICU of KTH appearing 1126 times in all the medication charts as shown in Table 3.17.

Table 3.17 Frequencies of commonly used drugs in SICU of KTH

Drug Name	Dosage Form	Frequency
Metronidazole	Intravenous	121
Ceftriaxone	Intravenous	119
Omeprazole	Intravenous	95
Ketorolac	Intravenous	93
Ranitidine	Intravenous	85
Dexamethasone	Intravenous	78
Valproate Sodium	Intravenous	69
Dimenhydrinate	Intravenous	59
Albuterol	Nebules	57
Piperacillin+Tazobactam	Intravenous	53
Tramadol	Intravenous	31
Enoxaparin	Subcutaneous	29
Clarithromycin	Intravenous	25
Ipratropium	Nebules	24
Cefoperazone+Sulbactam	Intravenous	23
Vancomycin	Intravenous	18
Amikacin	Intravenous	15
Meropenem	Intravenous	13
Dopamine	Intravenous	13
Imipenem+Cilastatin	Intravenous	11
Co-Amoxiclav	Intravenous	9
Beclomethasone	Nebules	9
Nimodipine	Tablets	8
Furosemide	Intravenous	7
Linezolid	Intravenous	5

Tranexamic Acid	Intravenous	5
Heparin	Subcutaneous	5
Nalbuphine	Intravenous	5
Lactulose	Syrup	4
Vitamin K	Intravenous	4
Gentamicin	Intravenous	4
Benzylpenicillin	Intravenous	3
Levetiracetam	Intravenous	3
Omeprazole	Tablets	3
Ceftizoxime	Intravenous	2
Ceftazidime	Intravenous	2
Nifedipine	Tablets	2
Domperidone	Syrups	2
Dobutamine	Intravenous	2
Ciprofloxacin	Intravenous	1
Moxifloxacin	Intravenous	1
Phenytoin	Intravenous	1
Cefotaxime	Intravenous	1
Metoclopramide	Intravenous	1
Hydrocortisone	Intravenous	1
Levofloxacin	Intravenous	1
Methyldopa	Tablets	1
Salmeterol+Fluticasone	Inhaler	1
Diclofenac Na	Intravenous	1
Azithromycin	Intravenous	1

3.1.2.8 Indications

Secondary infection was the most prevalent indication in the SICU of KTH (285 cases of 1126) followed by stress ulcer (182 cases), pain (121 cases), post-operative infection (119 cases), asthma (91 cases), seizures (67 cases), cerebral edema (63 cases), emesis (62 cases) and deep vein thrombosis (26 cases), while the rest of the cases were contributed by other indications.

3.1.2.9 Drug class

A total of 17 drug classes were used in the SICU of KTH with antibacterial being the most prevalent drug class as shown in Table 3.18.

Table 3.18 Frequencies of Drug classes used in SICU of KTH

Drug Class	Frequency
Antibacterial	424
Analgesic	120
PPI	97
Corticosteroid	88
H2 Receptor Antagonist	84
Bronchodilator	81
Anticonvulsant	68
Antiemetic	62
Anticoagulant	34
Vasopressor	15
Calcium Channel Blocker	8
Diuretic	7
Hemostatic	6
Laxative	4
Nutriceutical	2
Alpha Adrenergic Agonist	1
Clotting Activator	1

3.1.2.10 Dosing errors in SICU of KTH

Out of the total 1102 cases, 149 (13.5%) had subtherapeutic doses while 59 (5.4%) had overdoses as shown in Table 3.19 and Table 3.20 respectively.

Table 3.19 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Ranitidine	Intravenous	58
Piperacillin + Tazobactam	Intravenous	51
Imipenem + Cilastatin	Intravenous	8
Meropenem	Intravenous	6
Dexamethasone	Intravenous	6
Heparin	Subcutaneous	5
Nimodipine	Tablets	3
Ceftazidime	Intravenous	2
Gentamicin	Intravenous	2
Nalbuphine	Intravenous	2
Amikacin	Intravenous	2
Albuterol	Nebules	2
Phenytoin	Intravenous	1
Linezolid	Intravenous	1

Table 3.20 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Dexamethasone	Intravenous	30
Ranitidine	Intravenous	9
Enoxaparin	Subcutaneous	6
Clarithromycin	Intravenous	3
Beclomethasone	Nebules	3
Omeprazole	Intravenous	2
Tramadol	Intravenous	1
Meropenem	Intravenous	1
Vancomycin	Intravenous	1
Metronidazole	Intravenous	1
Albuterol	Nebules	1
Lactulose	Syrup	1

3.1.3 Hayatabad Medical Complex (HMC)

3.1.3.1 General Patient Characteristics

A total of 210 patients were analyzed in the SICU of HMC, of which 149 (71.0%) were males and 61 (29.0%) were females. The mean age of the population was 33.99 years and it ranged from 3 to 100 years. Patients of ages between 19 and 59 years were 66.2% while 18.6% of the patients were of 18 years and under, and 15.2% patients were of 60 years and above. Mean duration of stay in the critical care unit was 5.03 ± (3.80) days while the mean number of prescribed drugs were 5.57 ± (1.65) as shown in Table 3.21.

The top three leading causes of admission in the SICU of HMC were road traffic accident cases (RTA), laparotomy and craniotomy as shown in Figure 3.3.

Table 3.21 General Patient Characteristics in SICU of HMC

Variables	**Frequency (%)**
Gender	
Male	149 (71.0%)
Female	61 (29.0%)
Age (years)	
Mean ± SD	33.99 (± 19.41)
Median	30
Range	3-100
≤ 18	39 (18.6%)
19-59	139 (66.2%)
≥ 60	32 (15.2%)
Drugs prescribed per patient	
Mean ± SD	5.57 ± (1.65)
Median	5
Range	3-11
≤ 4	57 (27.2%)
5-6	104 (49.5%)
≥ 7	49 (23.3%)
Stay in ICU (days)	
Mean ± SD	5.03 ± (3.80)
Median	4
Range	1-28
≤ 2	39 (18.6%)
3-5	78 (37.1%)
≥ 6	93 (44.3%)

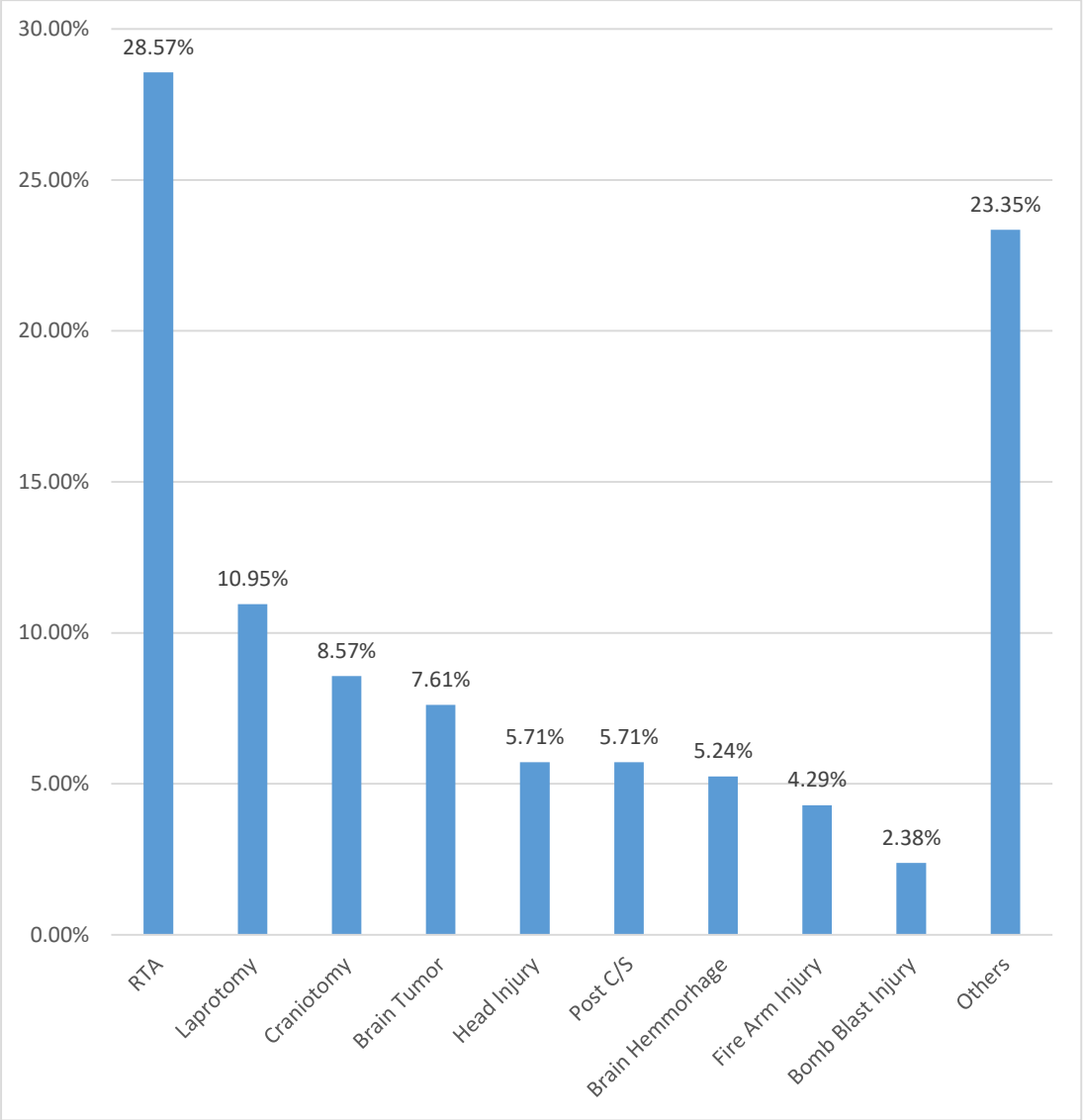

Figure 3.3 Causes of admission to SICU of HMC

3.1.3.2 Prevalence of Potential drug-drug interactions

The prevalence of PDDIs in patients of SICU of HMC was reported to be 38.6%. Of the total 210 patients, 55 patients had one PDDI, 13 patients had two PDDIs, 4 patients had three PDDIs, 8 patients had four PDDIs and 1 patient had seven PDDIs as shown in Table 3.22.

Table 3.22 Prevalence of PDDIs in SICU of HMC

No. Of PDDIs	Frequency	Percentage %
1	55	26.2
2	13	6.2
3	4	1.9
4	8	3.8
7	1	0.5

3.1.3.3 Categories of PDDIs

The PDDIs reported in the SICU of HMC were classified on the basis of severity, documentation and onset. The type and mechanisms of interactions were also identified. A total of 33 interacting drug pairs were identified which caused 132 drug-drug interactions. The severity of 64.4% PDDIs were major, 30.3% PDDIs were of moderate and 1.5% PDDIs were of minor severity while 3.8% were contraindicated. In terms of documentation 68.2% PDDIs were fairly documented, 8.3% PDDIs were of excellent and 23.5% PDDIs were of good documentation. The onset of 55.3% PDDIs were unknown, 35.6% PDDIs were of delayed and 9.1% PDDIs were of rapid onset. Of the total PDDIs, 18.9% were of pharmacodynamic type, 27.3% were of pharmacokinetic type while 53.8% were of unknown type. According to the mechanisms of PDDIs, synergism contributed to 16% of the PDDIs, antagonism contributed to 3% of the PDDIs, 24.2% PDDIs were due to metabolism, 3% PDDIs were due to elimination and 53.8% were of unknown mechanisms as shown in Table 3.23.

Table 3.23 Categories of PDDIs in SICU of HMC

Variable	Frequency (%)
Severity of PDDIs	
Major	85 (64.4%)
Moderate	40 (30.3%)
Minor	2 (1.5%)
Contraindicated	5 (3.8%)
Documentation of PDDIs	
Excellent	11 (8.3%)
Good	31 (23.5%)
Fair	90 (68.2%)
Onset of PDDIs	
Rapid	12 (9.1%)
Delayed	47 (35.6%)
Unkonwn	73 (55.3%)
Type of Interaction	
Pharmacodynamic	25 (18.9%)
Pharmacokinetic	36 (27.3%)
Unknown	71 (53.8%)
Mechanism of Interaction	
Synergism	21 (16.0%)
Antagonism	4 (3.0%)
Metabolism	32 (24.2%)
Elimination	4 (3.0%)
Unknown	71 (53.8%)

3.1.3.4 Interacting Drug Pairs

In the SICU of HMC, 33 interacting drug pairs were identified resulting in 132 drug-drug interactions. Of these interacting drug pairs, 7 were involved in 91 (68.9%) interactions of which 5 were major and 2 were moderate as shown in Table 3.24.

Table 3.24 Interacting drug pairs in SICU of HMC

Interacting pair	Frequency	Percentage %
ketorolac-valproate sodium	37	28%
clarithromycin-valproate	20	15.2%
meropenem-valproate	9	6.8%
clarithromycin-tramadol	7	5.3%
nimodipine-valproate	7	5.3%
enoxaparin-ketorolac	6	4.5%
dexamethasone-nimodipine	5	3.8%
clarithromycin-nimodipine	4	3%
ketorolac-nimodipine	4	3.0%
clarithromycin-dexamethasone	3	2.3%
amikacin-vancomycin	2	1.5%
imipenem-valproate sodium	2	1.5%
clarithromycin-nifedipine	2	1.5%
gentamicin-vancomycin	2	1.5%
cefoperazone-heparin	2	1.5%
clarithromycin-metronidazole	2	1.5%
genatamicin-piperacillin	2	1.5%

aspirin-enoxaparin	1	0.8%
aspirin-furosemide	1	0.8%
losartan-spironolactone	1	0.8%
aspirin-nitroglycerin	1	0.8%
arthemeter/lumefantrine-dexamethasone	1	0.8%
dexamethasone-rifampin	1	0.8%
amitriptyline-valproate	1	0.8%
albuterol-linezolid	1	0.8%
aspirin-losartan	1	0.8%
metoclopramide-tramadol	1	0.8%
aspirin-carvedilol	1	0.8%
aspirin-spironolactone	1	0.8%
valproic acid-isoniazid	1	0.8%
artemether/lumefantrine-clarithromycin	1	0.8%
salmeterol-linezolid	1	0.8%
rifampin-valproic acid	1	0.8%

3.1.3.5 Clinically significant PDDIs in SICU of HMC

Analysis of the drug interacting pairs for clinical significance yielded 16 pairs having a clinical significance of 1 and 2. These pairs contributed to 30.3% of the total PDDIs (40 of 132), 7 of which were of clinical significance 1 while 9 were of clinical significance 2. The clinically significant drug interacting pairs along with their potential outcomes are shown in Table 3.25.

Table 3.25 Clinically important interacting pairs and their potential outcomes in SICU of HMC

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Meropenem-valproate	1	9	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	96,97,98,99
Enoxaparin-ketorolac	1	6	Increased risk of bleeding.	100,101,102,103
Imipenem-valproate	1	2	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	104
Clarithromycin-Nifedipine	1	2	May result in increased nifedipine plasma concentrations	119
Aspirin-enoxaparin	1	1	Increased risk of bleeding.	105,106
Albuterol-Linezolid	1	1	Increased risk of cardiovascular adverse effects	116,117
Salmeterol-Linezolid	1	1	Increased risk of cardiovascular adverse effects	116,118
Nimodipine-valproate	2	7	Nimodipine toxicity (dizziness, headache, flushing, peripheral edema).	107
Dexamethasone-rifampin	2	1	May result in decreased dexamethasone effectiveness	120
Ketorolac-nimodipine	2	4	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	112,113

Aspirin-furosemide	2	1	May result in decreased diuretic and antihypertensive efficacy.	[121,122]
Aspirin-spironolactone	2	1	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.	[123]
Aspirin-carvedilol	2	1	May result in decreased antihypertensive effect.	[124,125]
Rifampin-valproic acid	2	1	May result in reduced valproate levels.	[126,28]
Aspirin-losartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-nitroglycerin	2	1	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	[128,129]

3.1.3.6 Association of PDDIs with other parameters in SICU of HMC

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

A significant association was found between the presence of PDDIs with the patients prescribed 5 or more drugs (OR = 32.919; 95%CI = 7.673-141.218; p = 0.000). An insignificant association was found between the presence of PDDIs and duration of stay of 4 or more days (OR = 1.476; 95%CI = 0.773-2.819; p = 0.238), and with gender (OR = 0.519; 95%CI = 0.259-1.039; p = 0.064) as shown in Table 3.26.

Table 3.26 logistic regression analysis in SICU of HMC

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=81)	**Interactions absent (n=129)**		
Prescribed drugs				
< 5	2	55		
≥ 5	79	74	32.919 (7.673-141.218)	0.000
Duration of stay				
< 4	28	53		
≥ 4	53	76	1.476 (0.773-2.819)	0.238
Gender				
Male	62	87		
Female	19	42	0.519 (0.259-1.039)	0.064

3.1.3.7 Drugs used

A total of 60 drugs were prescribed in the SICU of HMC appearing 1170 times in all the medication charts as shown in Table 3.27

Table 3.27 Frequencies of commonly used drugs in SICU of HMC

Drug Name	Dosage Form	Frequency
Metronidazole	Intravenous	110
Ceftriaxone	Intravenous	107
Omeprazole	Intravenous	96
Dexamethasone	Intravenous	91
Ranitidine	Intravenous	87
Valproate Sodium	Intravenous	86
Ketorolac	Intravenous	75
Albuterol	Nebules	64
Piperacillin+Tazobactam	Intravenous	50
Cefoperazone+Sulbactam	Intravenous	43
Clarithromycin	Intravenous	38
Amikacin	Intravenous	34
Ipratropium	Nebules	32
Tramadol	Intravenous	28
Vancomycin	Intravenous	25
Enoxaparin	Subcutaneous	23
Dimenhydrinate	Intravenous	23
Tranexamic Acid	Intravenous	17
Co-Amoxiclav	Intravenous	16
Imipenem+Cilastatin	Intravenous	12
Meropenem	Intravenous	11
Nimodipine	Tablets	9
Vitamin K	Intravenous	9
Lactulose	Syrups	8
Furosemide	Intravenous	6
Beclomethasone	Nebules	6
Heparin	Subcutaneous	5

Levetiracetam	Intravenous	5
Gentamicin	Intravenous	5
Ciprofloxacin	Intravenous	4
Linezolid	Intravenous	4
Moxifloxacin	Intravenous	3
Cefotaxime	Intravenous	3
Azithromycin	Intravenous	3
Terlipressin	Intravenous	2
Dopamine	Intravenous	2
Nifedipine	Tablets	2
Metoclopramide	Intravenous	2
Omeprazole	Tablets	2
Methyldopa	Tablets	2
Aspirin	Tablets	1
Furosemide+Spironolactone	Tablets	1
Losartan	Tablets	1
Cefepime	Intravenous	1
Benzylpenicillin	Intravenous	1
Nitroglycerin	Tablets	1
Colistimethate	Intravenous	1
Haloperidol	Tablets	1
Carvedilol	Tablets	1
Artemether+Lumefantrine	Tablets	1
Nalbuphine	Intravenous	1
Baclofen	Tablets	1
Captopril	Tablets	1
Rifmapin+Isoniazid+Pyrazinamide+Ethambutol	Tablets	1
Magnesium Sulfate	Intravenous	1
Sucralfate	Syrup	1
Salmeterol+Fluticasone	Inhaler	1
Metoclopramide	Tablets	1
Amitriptyline	Tablets	1
Gabapentin	Tablets	1

3.1.3.8 Indications

Secondary infection was the most prevalent indication in the SICU of HMC (347 cases of 1170) followed by stress ulcer (184 cases), post op infections (105 cases), asthma and pain (103 cases each), seizures (86 cases), cerebral edema (83 cases), emesis (26 cases) and deep vein thrombosis (19 cases), while the rest of the cases were contributed by other indications.

3.1.3.9 Drug class

A total of 29 drug classes were used in the SICU of HMC with antibacterial being the most prevalent drug class as shown in Table 3.28.

Table 3.28 Frequencies of Drug classes used in SICU of HMC

Drug Class	Frequency
Antibacterial	470
Analgesic	103
PPI	98
Corticosteroid	97
Bronchodilator	92
H2 Receptor Antagonist	87
Anticonvulsant	86
Anticoagulant	28
Antiemetic	26
Hemostatic	18
Calcium Channel Blocker	11
Nutriceutical	8
Laxative	8
Diuretic	7
Vasopressor	2
Alpha Adrenergic Agonist	2
Vasopressin	2
Antiplatelet	1
Beta Blocker	1
Anxiolytic	1
Ace Inhibitor	1
ARBs	1
Nitrates	1
Antimalarial	1
Mucosal Protective Agents	1
Antitubercular	1
Antipsychotic	1
Clotting Activator	1
Neuropathic Pain Agent	1

3.1.3.10 Dosing errors in the SICU of HMC

Out of the total 1157 cases, 177 (15.3%) had subtherapeutic doses while 43 (3.7%) had overdoses as shown in Table 3.29 and Table 3.30 respectively.

Table 3.29 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Ranitidine	Intravenous	78
Piperacillin + Tazobactam	Intravenous	47
Dexamethasone	Intravenous	13
Meropenem	Intravenous	9
Imipenem + Cilastatin	Intravenous	7
Amikacin	Intravenous	6
Heparin	Subcutaneous	5
Nimodipine	Tablets	3
Gentamicin	Intravenous	3
Co-amoxiclav	Intravenous	1
Metoclopramide	Intravenous	1
Linezolid	Intravenous	1
Baclofen	Tablets	1
Captopril	Tablets	1
Nitroglycerin	Tablets	1

Table 3.30 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Dexamethasone	Intravenous	14
Enoxaparin	Subcutaneous	6
Clarithromycin	Intravenous	5
Ranitidine	Intravenous	3
Tramadol	Nebules	3
Metronidazole	Intravenous	3
Beclomethasone	Nebules	3
Lactulose	Syrup	3
Ceftriaxone	Intravenous	1
Albuterol	Nebules	1
Sucralfate	Syrup	1

3.1.4 Northwest General Hospital and Research Center (NWGH & RC)

3.1.4.1 General Patient Characteristics

A total of 230 patients were analyzed in the SICU of NWGH & RC, of which 146 (63.5%) were males and 84 (36.5%) were females. The mean age of the population was 42.89 years and age of the patients ranged from 2 to 90 years, of which 62.2% patients were between the ages of 19 to 59 years, 27% were of 60 and above and 10.9% patients were of 18 years and below. Mean duration of stay in the critical care unit was 7.16 ± (5.25) days. While mean number of prescribed drugs were 6.02 ± (1.88) as shown in Table 3.31.

The top three leading causes of admission in the SICU of NWGH & RC were road traffic accident cases (RTA), brain hemorrhage and craniotomy as shown in Figure 3.4.

Table 3.31 General Patient Characteristics in SICU of NWGH & RC

Variables	**Frequency (%)**
Gender	
Male	146 (63.5%)
Female	84 (36.5%)
Age (years)	
Mean ± SD	42.89 (± 19.96)
Median	45
Range	2-90
≤ 18	25 (10.8%)
19-59	143 (62.2%)
≥ 60	62 (27.0%)
Drugs prescribed per patient	
Mean ± SD	6.02 ± (1.88)
Median	6
Range	2-14
≤ 4	40 (17.4%)
5-6	111 (48.3%)
≥ 7	79 (34.3%)
Stay in ICU (days)	
Mean ± SD	7.16 ± (5.25)
Median	6
Range	1-38
≤ 2	20 (8.7%)
3-5	47 (20.4%)
≥ 6	163 (70.9%)

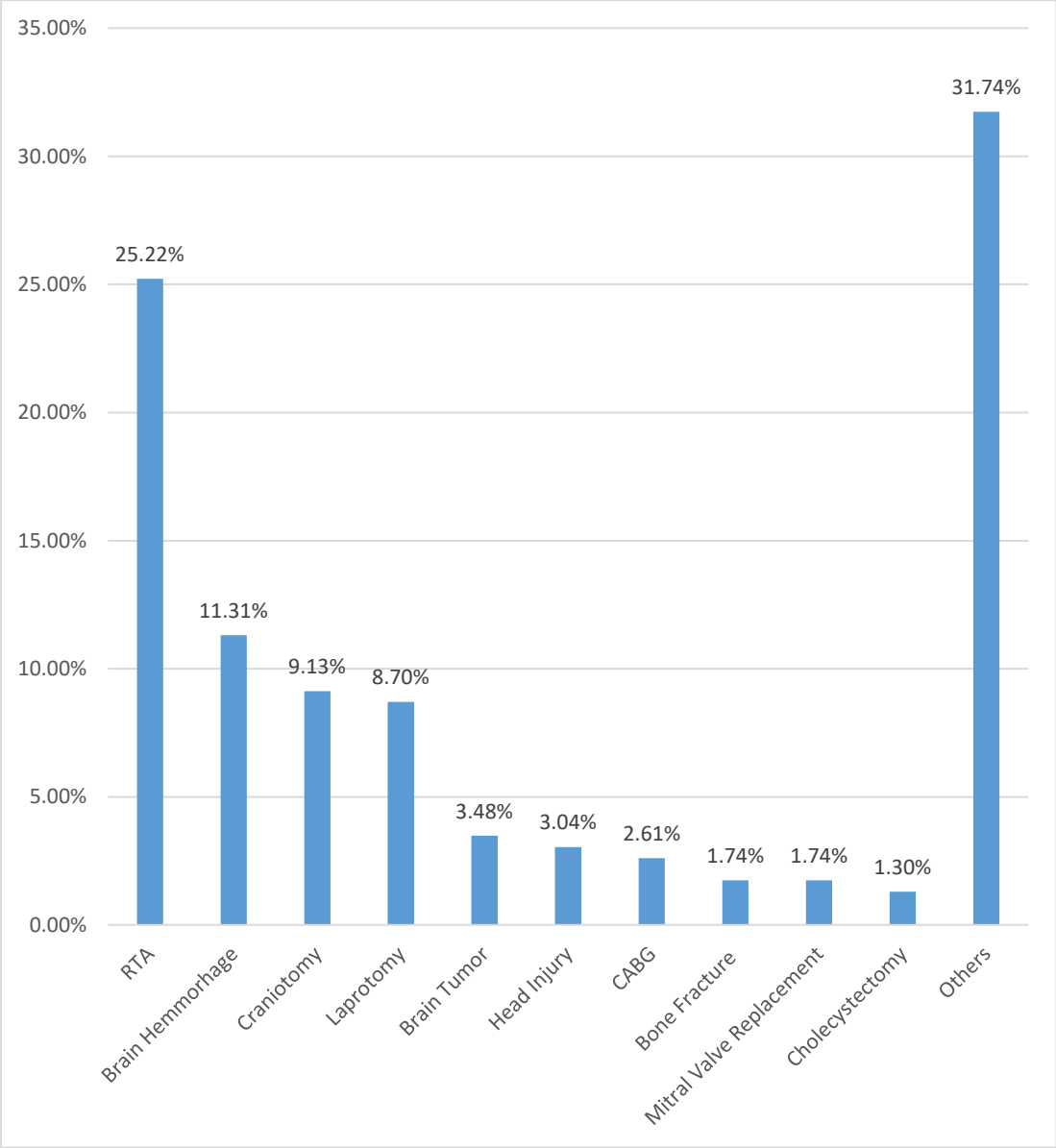

Figure 3.4 Causes of admission to SICU of NWGH & RC

3.1.4.2 Prevalence of Potential drug-drug interactions

The prevalence of PDDIs in patients of SICU of NWGH & RC was found to be 51.7%. Of the total 230 patients, 3 interactions were encountered by 14.8% of the patients while 0.9% of the patients had 8 interactions as shown in Table 3.32.

Table 3.32 Prevalence of PDDIs in SICU of NWGH & RC

No. Of PDDIs	Frequency	Percentage %
1	33	14.3
2	22	9
3	34	14.8
4	14	6.1
5	3	1.3
6	8	3.5
7	3	1.3
8	2	0.9

3.1.4.3 Categories of PDDIs

Severity, documentation, onset, type and mechanism of interactions were the parameters used to classify the PDDIs reported in the SICU of NWGH & RC. A total of 76 interacting drug pairs were identified resulting in 336 drug-drug interactions. According to severity 33.9% of the PDDIs were of major severity, 61.6% were of moderate, 3% were of minor severity and 1.5% were contraindicated PDDIs. Fairly documented PDDIs were 47.3%, 29.8% were of good and 22.9% were of excellent documentation. The onset of 33.3% PDDIs was unknown while 9.8% PDDIs were of rapid and 56.9% were of delayed onset. According to type of interactions, 24.7% PDDIs were of pharmacodynamic type and 59.2% PDDIs were of pharmacokinetic type while 16.1% were of unknown type. In terms of mechanism absorption contributed to 1.2% PDDIs, distribution contributed to 0.3% PDDIs, metabolism contributed to 54.8% PDDIs, elimination contributed to 3% PDDIs, synergism contributed to 21.1% PDDIs and antagonism contributed to 3.5% PDDIs while 16.1% were of unknown mechanisms as shown in Table 3.33.

Table 3.33 Categories of PDDIs in SICU of NWGH & RC

Variable	Frequency (%)
Severity of PDDIs	
Major	114 (33.9%)
Moderate	207 (61.6%)
Minor	10 (3.0%)
Contraindicated	5 (1.5%)
Documentation of PDDIs	
Excellent	77 (22.9%)
Good	100 (29.8%)
Fair	159 (47.3%)
Onset of PDDIs	
Rapid	33 (9.8%)
Delayed	191 (56.9%)
Unkonwn	112 (33.3%)
Type of Interaction	
Pharmacodynamic	83 (24.7%)
Pharmacokinetic	199 (59.2%)
Unknown	54 (16.1%)
Mechanism of Interaction	
Synergism	71 (21.1%)
Antagonism	12 (3.5%)
Absorption	4 (1.2%)
Distribution	1 (0.3%)
Metabolism	184 (54.8%)
Elimination	10 (3.0%)
Unknown	54 (16.1%)

3.1.4.4 Interacting Drug Pairs

In the SICU of NWGH & RC, 76 interacting drug pairs were identified resulting in 336 drug-drug interactions, of these interacting drug pairs, 6 were involved in 53.2% (179) interactions of which 3 were major and 3 were moderate as shown in Table 3.34.

Table 3.34 Interacting drug pairs in SICU of NWGH & RC

Interacting Pair	Frequency	Percentage
dexamethasone-phenytoin	61	18.2%
omeprazole-phenytoin	50	14.9%
ketorolac-phenytoin	28	8.3%
metronidazole-phenytoin	17	5.1%
dexamethasone-nimodipine	13	3.9%
enoxaparin-ketorolac	10	3.0%
atracurium-dexamethasone	7	2.1%
aspirin-clopidogrel	7	2.1%
phenytoin-ranitidine	7	2.1%
nimodipine-phenytoin	7	2.1%
aspirin-enoxaparin	6	1.8%
ketorolac-nimodipine	6	1.8%
aspirin-furosemide	5	1.5%
meropenem-valproate	5	1.5%
clopidogrel-enoxaparin	4	1.2%
ramipril-furosemide	4	1.2%
metoclopramide-tramadol	4	1.2%
amlodipine-dexamethasone	4	1.2%
amlodipine-ketorolac	4	1.2%
atracurium-gentamicin	3	0.9%
clarithromycin-phenytoin	3	0.9%
diclofenac-ketorolac	3	0.9%

aspirin-ramipril	3	0.9%
aspirin-bisoprolol	3	0.9%
tramadol-valproate sodium	3	0.9%
clarithromycin-dexamethasone	3	0.9%
clarithromycin-metronidazole	3	0.9%
amlodipine-phenytoin	3	0.9%
atorvastatin-clarithromycin	2	0.6%
aspirin-amlodipine	2	0.6%
clopidogrel-omeprazole	2	0.6%
aspirin-nitroglycerin	2	0.6%
dexamethasone-moxifloxacin	2	0.6%
aspirin-dexamethasone	2	0.6%
ciprofloxacin-metronidazole	2	0.6%
folic acid-phenytoin	2	0.6%
ceftriaxone-warfarin	2	0.6%
omeprazole-warfarin	2	0.6%
clopidogrel-ketorolac	2	0.6%
aspirin-ketorolac	2	0.6%
fluconazole-omeprazole	1	0.3%
digoxin-metoclopramide	1	0.3%
hydrocortisone-moxifloxacin	1	0.3%
enoxaparin-warfarin	1	0.3%
amiodarone-moxifloxacin	1	0.3%
clarithromycin-tramadol	1	0.3%
amlodipine-clarithromycin	1	0.3%
nimodipine-valproate	1	0.3%
aspirin-valsartan	1	0.3%
amlodipine-bisoprolol	1	0.3%
amlodipine-aspirin	1	0.3%
aspirin-hydrochlorothiazide	1	0.3%
spironolactone-warfarin	1	0.3%

aspirin-losartan	1	0.3%
clopidogrel-esomeprazole	1	0.3%
linezolid-tramadol	1	0.3%
metronidazole-moxifloxacin	1	0.3%
metronidazole-ondansetron	1	0.3%
esomeprazole-levothyroxine	1	0.3%
digoxin-omeprazole	1	0.3%
atracurium-phenytoin	1	0.3%
aspirin-nimodipine	1	0.3%
amiodarone-octreotide	1	0.3%
clarithromycin-warfarin	1	0.3%
paracetamol-warfarin	1	0.3%
ciprofloxacin-dexamethasone	1	0.3%
digoxin-tramadol	1	0.3%
clarithromycin-midazolam	1	0.3%
moxifloxacin-octreotide	1	0.3%
ketorolac-ramipril	1	0.3%
aspirin-prednisolone	1	0.3%
dexamethasone-warfarin	1	0.3%
ketorolac-valsartan	1	0.3%
phenytoin-midazolam	1	0.3%
midazolam-ranitidine	1	0.3%
tramadol-warfarin	1	0.3%

3.1.4.5 Clinically significant PDDIs in SICU of NWGH & RC

Analysis of the drug interacting pairs for clinical significance yielded 47 pairs having a clinical significance of 1 and 2. These pairs contributed to 49.7% of the total PDDIs (167 of 336), 11 of which were of clinical significance 1 while 36 were of clinical significance 2. The clinically significant drug interacting pairs along with their potential outcomes are shown in Table 3.35.

Table 3.35 Clinically important interacting pairs and their potential outcomes in SICU of NWGH & RC

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Meropenem-valproate	1	5	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	96,97,98,99
Enoxaparin-ketorolac	1	10	Increased risk of bleeding.	100,101,102,103
Aspirin-enoxaparin	1	6	Increased risk of bleeding.	105,106
Atorvastatin-clarithromycin	1	2	May result in increased atorvastatin exposure and an increased risk of myopathy or rhabdomyolysis.	130,131
Atracurium-gentamicin	1	3	May result in enhanced and/or prolonged neuromuscular blockade which may lead to respiratory depression and paralysis.	132,133
Linezolid-tramadol	1	1	May result in increased risk of serotonin syndrome (hyperthermia, hyperreflexia, myoclonus, mental status changes).	105,106
Clarithromycin-warfarin	1	1	Increased risk of bleeding.	134,135
Nimodipine-phenytoin	1	7	Reduced nimodipine plasma concentrations and efficacy.	107

Clopidogrel-omeprazole	1	2	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	[136,137]
Clopidogrel-esomeprazole	1	1	May result in reduced plasma concentrations of clopidogrel active metabolite.	[138,139]
Clopidogrel-ketorolac	1	2	Increased risk of bleeding.	[140]
Ketorolac-nimodipine	2	5	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112,113]
Aspirin-furosemide	2	5	May result in decreased diuretic and antihypertensive efficacy.	[121,122]
Aspirin-bisoprolol	2	3	May result in decreased antihypertensive effect.	[124,125]
Aspirin-losartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-valsartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-nitroglycerin	2	2	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	[128,129]
Aspirin-amlodipine	2	3	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[141]
Aspirin-prednisolone	2	1	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[114]

Aspirin-dexamethasone	2	2	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[142,115]
Aspirin-nimodipine	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[143,144]
Aspirin-hydrochlorothiazide	2	1	Decreased diuretic and antihypertensive efficacy.	[145]
Dexamethasone-warfarin	2	5	Increased risk of bleeding or diminished effects of warfarin.	[146]
Tramadol-warfarin	2	1	Increase in prothrombin time and an increased risk of bleeding.	[147,148]
Dexamethasone-phenytoin	2	61	Decreased dexamethasone effectiveness.	[109,110]
Atracurium-dexamethasone	2	7	Decreased atracurium effectiveness; prolonged muscle weakness and myopathy.	[149,150]
Ramipril-furosemide	2	3	May result in postural hypotension (first dose).	[151]
Amlodipine-bisoprolol	2	1	May result in hypotension and/or bradycardia.	[152,153]
Amlodipine-ketorolac	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[143,154]
Ketorolac-valsartan	2	1	Decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Phenytoin-midazolam	2	1	Decreased efficacy of midazolam.	[155]
Clarithromycin-phenytoin	2	3	Decreased clarithromycin plasma concentrations.	[126,156]

Omeprazole-warfarin	2	2	Elevations of INR values and potentiation of anticoagulant effects.	[157]
Ceftriaxone-warfarin	2	2	Increased risk of bleeding.	[158]
Nimodipine-valproate	2	1	Nimodipine toxicity (dizziness, headache, flushing, peripheral edema).	[107]
Paracetamol-warfarin	2	1	Increased risk of bleeding.	[159,160]
Digoxin-tramadol	2	1	Increased risk of digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[147,161]
Clarithromycin-midazolam	2	1	Increased triazolobenzodiazepine exposure resulting in increased and prolonged sedation.	[162,163]
Ketorolac-ramipril	2	1	May result in renal dysfunction or decreased antihypertensive efficacy.	[164]
Dexamethasone-moxifloxacin	2	2	Increased risk of tendon rupture.	[165]
Digoxin-omeprazole	2	1	Increased risk of digoxin toxicity (nausea, vomiting, arrhythmias).	[166]
Folic acid-phenytoin	2	1	Decreased folic acid serum levels; decreased phenytoin effectiveness.	[167,168]
Ciprofloxacin-dexamethasone	2	1	Increased risk of tendon rupture.	[169]

Fluconazole-omeprazole	2	1	May result in increased plasma concentrations of omeprazole.	[170]
Digoxin-metoclopramide	2	1	May result in decreased digoxin levels.	[171,172]
Hydrocortisone-moxifloxacin	2	1	Increased risk of tendon rupture.	[165]
Esomeprazole-levothyroxine	2	1	May result in increased TSH levels.	[173,174]

3.1.4.6 Association of PDDIs with other parameters in SICU of NWGH & RC

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

A significant association was found between the presence of PDDIs with the patients prescribed 6 or more drugs (OR = 8.211; 95%CI = 4.483-15.037; p = 0.000). An insignificant association was found between the presence of PDDIs and duration of stay of 4 or more days (OR = 1.216; 95%CI = 0.552-2.677; p = 0.627), and with gender (OR = 0.847; 95%CI = 0.459-1.563; p = 0.596) as shown in Table 3.36.

Table 3.36 logistic regression analysis in SICU of NWGH & RC

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=119)	**Interactions absent (n=111)**		
Prescribed drugs				
< 6	23	74		
≥ 6	96	37	8.211 (4.483-15.037)	0.000
Duration of stay				
< 4	17	23		
≥ 4	102	88	1.216 (0.552-2.677)	0.627
Gender				
Male	78	68		
Female	41	43	0.847 (0.459-1.563)	0.596

3.1.4.7 Drugs used

A total of 99 drugs were prescribed in the SICU of NWGH & RC appearing 1381 times in all the medication charts as shown in Table 3.37.

Table 3.37 Frequencies of commonly used drugs in SICU of NWGH & RC

Drug Name	Dosage Form	Frequency
Ceftriaxone	Intravenous	141
Omeprazole	Intravenous	139
Dexamethasone	Intravenous	109
Dimenhydrinate	Intravenous	92
Metronidazole	Intravenous	76
Ketorolac	Intravenous	69
Phenytoin	Intravenous	62
Metoclopramide	Intravenous	60
Tramadol	Intravenous	52
Co-Amoxiclav	Intravenous	41
Enoxaparin	Subcutaneous	41
Ranitidine	Intravenous	38
Esomeprazole	Intravenous	33
Meropenem	Intravenous	30
Imipenem+Cilastatin	Intravenous	28
Cefoperazone+Sulbactam	Intravenous	27
Albuterol	Nebules	25
Ipratropium	Nebules	19
Nimodipine	Tablets	16
Piperacillin+Tazobactam	Intravenous	15
Atracurium	Intravenous	13
Cefotaxime	Intravenous	12
Amlodipine	Tablets	12
Furosemide	Intravenous	11
Clarithromycin	Intravenous	11

Nalbuphine	Intravenous	11
Propofol	Intravenous	11
Aspirin	Tablets	9
Moxifloxacin	Intravenous	9
Valproate Sodium	Intravenous	8
Beclomethasone	Nebules	8
Rosuvastatin	Tablets	7
Tranexamic Acid	Intravenous	7
Cefuroxime	Intravenous	7
Lactulose		7
Gentamicin	Intravenous	7
Ciprofloxacin	Intravenous	6
Vancomycin	Intravenous	6
Ramipril	Tablets	5
Linezolid	Intravenous	5
Clopidogrel+Aspirin	Tablets	4
Losartan	Tablets	4
Carvedilol	Tablets	4
Diclofenac Na	Intravenous	4
Vitamin K	Intravenous	4
Clopidogrel	Tablets	3
Bisoprolol	Tablets	3
Colistimethate	Intravenous	3
Nifedipine	Tablets	3
Ondansetron	Intravenous	3
Valsartan	Tablets	2
Cefepime	Intravenous	2
Nitroglycerin	Tablets	2
Rifaximin	Tablets	2
Atorvastatin	Tablets	2
Omeprazole	Tablets	2
Warfarin	Tablets	2
Ferrous Sulfate+Folic Acid	Tablets	2

Calcitriol	Intravenous	2
Calcium Gluconate	Intravenous	2
Domperidone	Syrup	2
Phenytoin	Tablets	2
Digoxin	Tablets	1
Montelukast	Tablets	1
Metoprolol	Tablets	1
Valsartan+Hydrochlorothiazide	Tablets	1
Furosemide+Spironolactone	Tablets	1
Amiodarone	Tablets	1
Cefixime	Tablets	1
Prednisolone	Tablets	1
Dopamine	Intravenous	1
Isosorbide Mononitrate	Tablets	1
Atenolol	Tablets	1
Heparin	Subcutaneous	1
Ceftazidime	Intravenous	1
Levofloxacin	Tablets	1
Bosentan	Tablets	1
Hydrocortisone	Intravenous	1
Clarithromycin	Syrup	1
Folic Acid	Tablets	1
Octreotide	Subcutaneous	1
Gliclazide	Tablets	1
Trimetazidine	Tablets	1
Esomeprazole	Tablets	1
Domperidone	Tablets	1
Nicorandil	Tablets	1
Sucralfate	Syrup	1
Moxifloxacin	Tablets	1
Fluconazole	Intravenous	1
Thyroxine	Tablets	1
Rabeprazole	Tablets	1

Pregabalin	Tablets	1
Paracetamol	Tablets	1
Doxycycline	Tablets	1
Norepinephrine	Intravenous	1
Bicalutamide	Tablets	1
Labetalol	Intravenous	1
Midazolam	Intravenous	1
Sulfamethoxazole+Trimethoprim	Tablets	1

3.1.4.8 Indications

Secondary infection was the most prevalent indication in the SICU of NWGH & RC (253 cases of 1381) followed by stress ulcer (212 cases), emesis (158 cases), post-operative infections (139 cases), pain (137 cases), cerebral edema (104 cases), seizures (72 cases), asthma (45 cases) and deep vein thrombosis (37 cases), while the rest of the cases were contributed by other indications.

3.1.4.9 Drug class

A total of 39 drug classes were used in the SICU of NWGH & RC with antibacterial being the most prevalent drug class as shown in Table 3.38.

Table 3.38 Frequencies of Drug classes used in SICU of NWGH & RC

Drug Class	Frequency
Antibacterial	434
Proton Pump Inhibitors	176
Antiemetic	158
Analgesic	137
Corticosteroid	119
Anticonvulsant	72
Anticoagulant	48
Bronchodilator	45
H2 Receptor Antagonist	37
Calcium Channel Blocker	31
Musculoskeletal Agent	13
Antiplatelet	12
Diuretic	12
Sedative	11
Beta Blocker	10
HMG Co A Reductase Inhibitor	9
Arbs	7
Hemostatic	6
Ace Inhibitor	5
Nutriceutical	5
Laxative	5
Nitrates	3
Antianemic	3
Clotting Activator	3
Vasopressor	2
Liver Protectant	2
Anti Ischemic Agent	2
Cardiac Glycoside	1
Antifungal	1

Leukotriene Receptor Antagonist	1
Antiarrhythmic	1
Antithyroid Agent	1
Endothelial Receptor Antagonist	1
Sulfonyl Ureas	1
Hormone	1
Mucosal Protective Agnets	1
Neuropathic Pain Agent	1
Antiandrogen	1
Antiplasminic Agent	1

3.1.4.10 Dosing errors in SICU of NWGH & RC

Out of the total 1380 cases, 98 (7.1%) had subtherapeutic doses while 59 (4.3%) had overdoses as shown in Table 3.39 and Table 3.40 respectively.

Table 3.39 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Ranitidine	Intravenous	24
Dexamethasone	Intravenous	23
Nimodipine	Tablets	12
Imipenem + Cilastatin	Intravenous	7
Co-amoxiclav	Intravenous	7
Piperacillin + Tazobactam	Intravenous	6
Meropenem	Intravenous	4
Gentamicin	Intravenous	3
Phenytoin	Tablets	2
Nitroglycerin	Tablets	2
Albuterol	Nebules	2
Octreotide	Subcutaneous	1
Ciprofloxacin	Intravenous	1
Nalbuphine	Intravenous	1
Metoclopramide	Intravenous	1
Warfarin	Tablets	1
Trimetazidine	Tablets	1

Table 3.40 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Dexamethasone	Intravenous	17
Enoxaparin	Subcutaneous	5
Phenytoin	Intravenous	4
Ipratropium	Nebules	4
Amlodipine	Tablets	3
Nifedipine	Tablets	3
Albuterol	Nebules	3
Furosemide	Intravenous	2
Diclofenac sodium	Intravenous	2
Cefuroxime	Intravenous	2
Beclomethasone	Nebules	2
Sucralfate	Syrup	1
Ceftriaxone	Intravenous	1
Co-amoxiclav	Intravenous	1
Moxifloxacin	Intravenous	1
Cefotaxime	Intravenous	1
Omeprazole	Intravenous	1
Ketorolac	Intravenous	1
Calcium gluconate	Intravenous	1
Nalbuphine	Intravenous	1
Fluconazole	Intravenous	1
Tranexamic acid	Intravenous	1
Rifaximin	Tablets	1

3.1.5 Comparison of PDDIs among the hospitals

One-way ANOVA revealed a significant difference (p=0.000) in the means of PDDIs among the four hospitals. Post HOC test (LSD) revealed that there was a significant difference (p=0.000) of PDDIs between NWGH & RC and the other three hospitals (LRH, KTH & HMC).

3.1.6 DISCUSSION

Critical nature of patients in surgical intensive care units (SICU) make them particularly vulnerable to the risk of potential drug-drug interactions due to complication of the severity of the disease and organ failure. Studies are also limited in this area making the patients even at a higher risk.

The prevalence of potential drug-drug interactions (PDDIs) were found to be higher in private setup. An average of 34.1% PDDIs were found to occur in government setup while 56.7% PDDIs occurred in the private hospital. This is due to the fact that government setups has lesser number of drugs prescribed as compared to the private setup along with the shorter duration of stay of the patients in critical care unit and lesser mean age of the patients.

A Brazilian study conducted in a teaching hospital reported the prevalence of drug-drug interactions to be 10.6% in emergency surgeries.[175] Another Brazilian study conducted in SICU of a tertiary care hospital reported 55% of the patients had at least one PDDI.[74] An Iranian study, PPDIs prevalence was reported to be 20.3% in patients admitted to a hospital.[65] A cancer center in USA reported a 7.3% prevalence of PDDIs in the 275 patients admitted during the research period.[77] While another study conducted in the SICU in USA observed a prevalence of PDDIs in 26.6% patients.[77]

This study complies with some studies, which report a similar prevalence of PDDIs but other studies reported a lower rate of PDDIs. This difference is due to the better monitoring and health care system along with the presence of interventional strategies to prevent PDDIs in well-developed hospitals.

The number of interacting drug pairs and potential drug-drug interactions were reported to be low in the government hospitals as compared to the private hospital. The severity of most interactions in the government hospitals were major (76.2%, 72.9%, 64.4% in LRH, KTH and HMC respectively) while in the private hospital most PDDIs were of moderate severity (61.6%). Similarly, onset and the type of interactions of most of the PDDIs encountered in the government hospital was unknown as compared to delayed onset and pharmacokinetic type in the private hospital. This difference was mostly due to the fact that phenytoin was more commonly used in the SICU of the private hospital for seizures as compared to sodium valproate which was used in the government hospitals, and sodium valproate comparatively has lesser potential for drug interactions.

A retrospective study reported that PDDIs of major severity were most common (34%) as compared to moderate (27%)[69] while another study reported PDDIs of moderate severity to be dominant, 78% as compared to 12.8% of major severity.[176] A Swedish study reported interactions of moderate severity to be the most common (23%) as well.[51]

A significant association was found between number of interactions and number of prescribed drugs in this study. Various other studies have also reported a similar association. An Ethiopian study revealed a significant association between these two factors when patient received three or more drugs.[177] Another Indian study reported a significant positive association between these two factors.[178] While various Pakistani,

Iranian, Brazilian, Italian, Swedish and American studies also reported a significant association between number of interactions and number of prescribed drugs.[81,84,63,59,179] No significant association was found between duration of stay and number of interactions. A similar non-significant association was reported in another study conducted in an ICU of a university hospital.[180] Some studies suggested a significant association of hospital stay with the number of interactions.[81,84] A possible reason behind the insignificant association between number of interactions and duration of stay found in this study may be the shorter duration of stay of patients in the critical care units as compared to other worldwide studies.

Anticonvulsants, antibiotics and NSAIDs were the drugs involved in maximum number of PDDIs in the SICU. Other studies also reported involvement of these drugs in majority of PDDIs.[181,65]

The potentially significant drug-drug interactions can be managed and the risk of adverse effects be minimized by following proper guidelines.

3.1.7 Management guidelines for clinically significant PDDIs

Potential drug-drug interactions having a severity of major or moderate with excellent or good documentation were considered clinically significant and were rated values as 1 and 2. Using these criteria along with the frequency of PDDIs, a list of 9 interacting drug pairs was considered important clinically, because of the associated high risk and occurrence in the surgical intensive care units.

3.1.7.1 Sodium Valproate + Imipenem/Meropenem

The concurrent use of valproate and meropenem or imipenem may reduce the plasma concentrations of valproate reducing its anticonvulsant effect. The mechanism for this interaction is unknown but its clinical significance is high. Increasing the dose of valproate is not recommended because it may still not be enough to achieve therapeutic concentrations in the plasma. So it is recommended to use an alternative antibiotic which has no effect on the plasma concentrations of valproate. However, if it concurrent administration is required, other anticonvulsants should be added to the therapy.[99,96,98]

3.1.7.2 Enoxaparin + Ketorolac

The combination of enoxaparin and ketorolac may increase the risk of bleeding. In patients receiving spinal anesthesia or undergoing a spinal puncture, the drug combination may cause epidural or spinal hematomas. Synergistic mechanism is involved in this interaction as the drugs decrease platelet activity and coagulation. Recommendation include to stop the administration of ketorolac before initiating enoxaparin therapy. If simultaneous administration cannot be avoided, then patient should be monitored for signs and symptoms of bleeding.[103]

Aspirin + Enoxaparin

The concomitant use of aspirin and enoxaparin results of an increased risk of bleeding. In patients receiving spinal anesthesia or undergoing a spinal puncture, the drug combination may cause epidural or spinal hematomas. However, it is used in myocardial infarction and ischemic conditions of the heart where this PDDI may be considered as beneficial, because of its synergistic action on decreasing platelet

function and coagulation. Patients should be monitored closely for any sign and symptom of bleeding and treated accordingly otherwise.[102,100]

3.1.7.3 Nimodipine + Valproate Sodium

Simultaneous administration of nimodipine and valproate may lead to nimodipine toxicity displayed by dizziness, headache, flushing and peripheral edema. Decreased metabolism of nimodipine is responsible for this interaction and downward adjustment of the dose of nimodipine is required in this case.[107]

3.1.7.4 Ketorolac + Nimodipine

Concurrent use of ketorolac and nimodipine may lead to increased risk of gastrointestinal bleeding along with antagonism of hypotensive effect. Decreased production of renal prostaglandin is the mechanism responsible for this interaction. Patient should be monitored for signs and symptoms of gastrointestinal bleeding like weakness, nausea and blood in stool, monitoring of patient blood pressure is also advised.[182,143,183]

3.1.7.5 Nimodipine + Phenytoin

Concomitant use of nimodipine with phenytoin may reduce its plasma concentrations and efficacy, reducing its antihypertensive effect. Phenytoin increases the metabolism of nimodipine by inducing CYP3A4 enzymes thus decreasing its plasma concentrations. Concurrent use of these two drugs must be avoided and one of the either two replaced by a suitable substituent.[184,185]

3.1.7.6 Dexamethasone + Phenytoin

Dexamethasone effectiveness may be decreased when used in combination with phenytoin due to the increased metabolism of dexamethasone in the presence of phenytoin. Monitoring of the therapeutic effect of dexamethasone is recommended and a 2 times or more increase in the dose of dexamethasone may be required. Phenytoin plasma concentrations should also be monitored as it can also be altered.[186]

3.1.7.7 Atracurium + Dexamethasone

Using dexamethasone with atracurium may decrease the efficacy of atracurium causing prolonged muscle weakness and myopathy. During concurrent therapy the effectiveness of atracurium should be monitored especially when high doses of dexamethasone is administered. In patients receiving prolonged combination therapy of these two drugs, it is recommended to allow un-paralyzed periods to decrease the total dose of atracurium. The mechanism of this interaction is unknown and further pharmacokinetic studies can highlight the probable mechanism.[187]

3.2 MEDICAL INTENSIVE CARE UNIT (MICU)

3.2.1 Lady Reading Hospital (LRH)

3.2.1.1 General Patient Characteristics

In the MICU of LRH a total of 210 patients were analyzed, of which 90 (42.9%) were males and 120 (57.1%) were females. The mean age of the patients was 36.45 years and ranged from 11 to 88 years. Of the total patients, 69.1% patients were between the ages of 19 to 59 years, 15.2% were of 18 years and below, while 15.7% patients were of 60 years and above. Mean duration of stay in the critical care unit and mean number of prescribed drugs were 4.6 ± (3.18) days and 5.38 ± (1.85) drugs respectively as shown in Table 3.41.

The top three leading causes of admission in the MICU or LRH were tetanus, septicemia, post natal sepsis and diabetic ketoacidosis as shown in Figure 3.5.

Table 3.41 General Patient Characteristics in the MICU of LRH

Variables	**Frequency (%)**
Gender	
Male	90 (42.9%)
Female	120 (57.1%)
Age (years)	
Mean ± SD	36.45 (± 17.90)
Median	30
Range	11-88
≤ 18	32 (15.2%)
19-59	145 (69.1%)
≥ 60	33 (15.7%)
Drugs prescribed per patient	
Mean ± SD	5.38 ± (1.85)
Median	5
Range	2-11
≤ 4	71 (33.8%)
5-6	87 (41.4%)
≥ 7	52 (24.8%)
Stay in ICU (days)	
Mean ± SD	4.60 ± (3.18)
Median	4
Range	1-21
≤ 2	48 (22.9%)
3-5	82 (39.0%)
≥ 6	80 (38.1%)

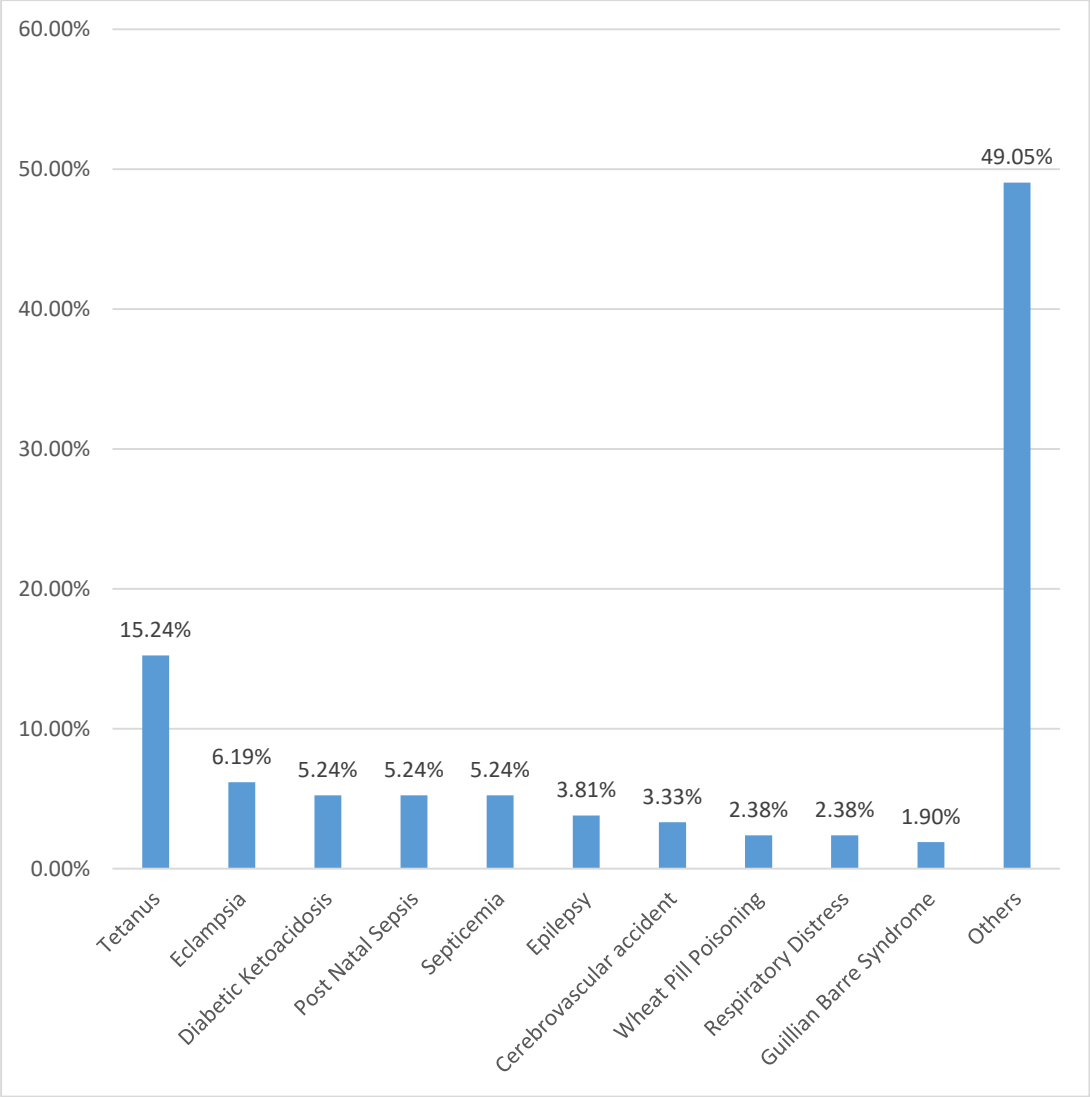

Figure 3.5 Causes of admission to MICU of LRH

3.2.1.2 Prevalence of Potential drug-drug interactions

A prevalence of 36.7% PDDIs was reported in the patients of MICU of LRH. Forty two patients encountered one PDDI, twenty three patients encountered two PDDIs, five patients encountered three PDDIs and three patients encountered four PDDIs, while two patients each encountered five and seven PDDIs as shown in Table 3.42.

Table 3.42 Prevalence of PDDIs in the MICU of LRH

No. of PDDIs	Frequency	Percentage %
1	42	20.0
2	23	11
3	5	2.4
4	3	1.4
5	2	1.0
7	2	1.0

3.2.1.3 Categories of PDDIs

The PDDIs reported in the MICU of LRH were classified on the basis of severity, documentation, onset and clinical significance. The type and mechanisms of interactions were also identified. A total of 53 interacting drug pairs were identified which caused 139 drug-drug interactions. The severity of 59.0% PDDIs were major, 25.2% PDDIs were of moderate and 15.8% of the PDDIs were of minor severity. The documentation of 50.4% PDDIs was fair, 41.7% PDDIs were of good and 7.9% of the PDDIs were of excellent documentation. According to the onset of PDDIs, 11.5% were of rapid onset, 34.5% were of delayed onset while 54% were of unknown onset. In terms of type of PDDIs, pharmacokinetics and pharmacodynamics were involved in 49.6% and 48.2% PDDIs, while 2.2% PDDIs were of unknown type. In terms of mechanism, synergism was involved in 45.3% PDDIs, antagonism was involved in 2.9% PDDIs, absorption contributed to 8.6% PDDIs, distribution was involved in 0.7% PDDIs, metabolism contributed for 35.3% PDDIs, elimination contributed in 5% PDDIs, while 2.2% PDDIs were of unknown mechanisms. The results are shown in Table 3.43.

Table 3.43 Categories of PDDIs in the MICU of LRH

Variable	Frequency (%)
Severity of PDDIs	
Major	82 (59.0%)
Moderate	35 (25.2%)
Minor	22 (15.8%)
Documentation of PDDIs	
Excellent	11 (7.9%)
Good	58 (41.7%)
Fair	70 (50.4%)
Onset of PDDIs	
Rapid	16 (11.5%)
Delayed	48 (34.5%)
Unkonwn	75 (54.0%)
Type of Interaction	
Pharmacodynamic	67 (48.2%)
Pharmacokinetic	69 (49.6%)
Unknown	3 (2.2%)
Mechanism of Interaction	
Synergism	63 (45.3%)
Antagonism	4 (2.9%)
Absorption	12 (8.6%)
Distribution	1 (0.7%)
Metabolism	49 (35.3%)
Elimination	7 (5%)
Unknown	3 (2.2%)

3.2.1.4 Interacting Drug Pairs

In the MICU of LRH, 53 interacting drug pairs were identified causing 139 drug-drug interactions, of these interacting drug pairs, 5 were involved in 60 (43.17%) interactions of which 3 were major and 2 were moderate as shown in Table 3.44.

Table 3.44 Interacting drug pairs in the MICU of LRH

Interacting pair	Frequency	Percentage
metronidazole-tizanidine	20	14.4%
diazepam-omeprazole	15	10.8%
clarithromycin-metronidazole	10	7.2%
acyclovir-valproate sodium	9	6.5%
clopidogrel-enoxaparin	6	4.3%
clarithromycin-nifedipine	5	3.6%
clarithromycin-dexamethasone	5	3.6%
aspirin-dexamethasone	5	3.6%
aspirin-clopidogrel	4	2.9%
aspirin-enoxaparin	4	2.9%
metronidazole-quinine	4	2.9%
clopidogrel-omeprazole	3	2.2%
piperacillin/tazobactam+streptomycin	3	2.2%
albuterol-bisoprolol	2	1.4%
aspirin-bisoprolol	2	1.4%
iron sucrose-omeprazole	2	1.4%
dexamethasone-nifedipine	2	1.4%
amoxicillin-streptomycin	2	1.4%
metronidazole-moxifloxacin	2	1.4%
dexamethasone-nimodipine	1	0.7%
enoxaparin-ketorolac	1	0.7%
aspirin-ranitidine	1	0.7%

clarithromycin-tramadol	1	0.7%
aspirin-furosemide	1	0.7%
ramipril-furosemide	1	0.7%
dexamethasone-rifampin	1	0.7%
clarithromycin-valproate	1	0.7%
captopril-furosemide	1	0.7%
citalopram-omeprazole	1	0.7%
carbamazepine-dexamethasone	1	0.7%
ramipril-spironolactone	1	0.7%
dexamethasone-levofloxacin	1	0.7%
artemether/lumefantrine-metronidazole	1	0.7%
amikacin-furosemide	1	0.7%
carbamazepine-clarithromycin	1	0.7%
valproic acid-isoniazid	1	0.7%
enalapril-spironolactone	1	0.7%
carbamazepine-metronidazole	1	0.7%
levofloxacin-piroxicam	1	0.7%
metoprolol-nifedipine	1	0.7%
prochlorperazine-quinine	1	0.7%
clarithromycin-quinine	1	0.7%
azithromycin-quinine	1	0.7%
clarithromycin-rifaximin	1	0.7%
clarithromycin-methylprednisolone	1	0.7%
nifedipine-valproate sodium	1	0.7%
rifampin-valproic acid	1	0.7%
enalapril-furosemide	1	0.7%
metoprolol-ranitidine	1	0.7%
metronidazole-prochlorperazine	1	0.7%
amikacin-piperacillin	1	0.7%
clarithromycin-diazepam	1	0.7%
rifampin-omeprazole	1	0.7%

3.2.1.5 Clinically significant PDDIs in the MICU of LRH

Analysis of the drug interaction pairs for clinical significance yielded 23 pairs having a clinical significance 1 or 2. These pairs contributed to 33.8% of the total PDDIs (47 of 139) of which 18 were of clinically significance 1 while 29 were of clinical significance 2. The clinically significant drug interaction pairs along with their potential outcomes are shown in Table 3.45.

Table 3.45 Clinically important interacting pairs and their potential outcomes in the MICU of LRH

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Enoxaparin-ketorolac	1	1	Increased risk of bleeding.	100, 101,102,103
Clarithromycin-Nifedipine	1	5	May result in increased nifedipine plasma concentrations	119
Aspirin-enoxaparin	1	4	Increased risk of bleeding.	105,106
Clopidogrel-omeprazole	1	3	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	188
Ramipril-spironolactone	1	1	May result in hyperkalemia.	189,190
Enalapril-spironolactone	1	1	May result in hyperkalemia.	189,190
Dexamethasone-nifedipine	1	2	May result in decreased nifedipine exposure	191
Carbamazepine-clarithromycin	1	1	May result in decreased exposure of clarithromycin; increased exposure of carbamazepine.	192
Clarithromycin-methylprednisolone	2	1	Increased risk of methylprednisolone adverse effects	192
Ramipril-furosemide	2	1	May result in postural hypotension (first dose).	151
Enalapril-furosemide	2	1	May result in postural hypotension (first dose).	151
Captopril-furosemide	2	1	May result in postural hypotension (first dose).	151
Dexamethasone-rifampin	2	1	May result in decreased dexamethasone effectiveness	120

Aspirin-dexamethasone	2	5	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[142,115]
Aspirin-furosemide	2	1	May result in decreased diuretic and antihypertensive efficacy.	[121,122]
Dexamethasone-levofloxacin	2	1	Increased risk of tendon rupture.	[165]
Aspirin-bisoprolol	2	2	May result in decreased antihypertensive effect.	[124,125]
Rifampin-valproic acid	2	1	May result in reduced valproate levels.	[126,28]
Clarithromycin-diazepam	2	1	May result in increased benzodiazepine toxicity (CNS depression, ataxia, lethargy).	[193]
Iron sucrose-omeprazole	2	2	May result in reduced non-heme iron bioavailability.	[194]
Acyclovir-valproic acid	2	9	Decreased valproic acid plasma concentrations and potential increased seizure activity.	[195]
Carbamazepine-metronidazole	2	1	Increased carbamazepine serum concentrations and potential carbamazepine toxicity.	[196]
Metoprolol-nifedipine	2	1	May result in hypotension and/or bradycardia	[197]

3.2.1.6 Association of PDDIs with other parameters in the MICU of LRH

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 5 or more drugs (OR = 23.305; 95%CI = 6.862-79.150; p = 0.000), and with gender (OR = 0.420; 95%CI = 0.214-0.824; p = 0.012). An insignificant association was found between the presence of PDDIs and duration of stay of 4 or more days (OR = 0.966; 95%CI = 0.480-1.945; p = 0. 923). The results are shown in Table 3.46.

Table 3.46 logistic regression analysis in the MICU of LRH

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=77)	**Interactions absent (n=133)**		
Prescribed drugs				
< 5	3	68		
≥ 5	74	65	23.305 (6.862-79.150)	0.000
Duration of stay				
< 4	27	68		
≥ 4	50	65	0.966 (0.480-1.945)	0.923
Gender				
Male	46	44		
Female	31	89	0.420 (0.214-0.824)	0.012

3.2.1.7 Drugs used

A total of 96 drugs were prescribed in the MICU of LRH appearing 1129 times in all the medication charts as shown in Table 3.47.

Table 3.47 Frequencies of commonly used drugs in the MICU of LRH

Drug Name	Dosage Form	Frequency
Metronidazole	Intravenous	156
Omeprazole	Intravenous	123
Piperacillin+tazobactam	Intravenous	86
Ceftriaxone	Intravenous	76
Albuterol	Nebules	60
Ranitidine	Intravenous	54
Dexamethasone	Intravenous	52
Enoxaparin	Subcutaneous	37
Lactulose	Syrup	35
Benzylpenicillin	Intravenous	33
Tizanidine	Tablets	29
Ipratropium	Nebules	24
Valproate sodium	Intravenous	21
Beclomethasone	Nebules	21
Clarithromycin	Intravenous	19
Acyclovir	Intravenous	17
Diazepam	Intravenous	17
Vitamin K	Intravenous	14
Esomeprazole	Intravenous	13
Paracetamol+Orphenadrine	Tablets	19
Cefoperazone+Sulbactam	Intravenous	12
Quinine	Intravenous	12
Dopamine	Intravenous	10
Meropenem	Intravenous	9
Co-amoxiclav	Intravenous	8

Nifedipine	Tablets	8
Furosemide	Intravenous	7
Dimenhydrinate	Intravenous	7
Tranexamic acid	Intravenous	7
Diazepam	Tablets	7
Levofloxacin	Intravenous	6
Rosuvastatin	Tablets	5
Clopidogrel	Tablets	5
Ramipril	Tablets	5
Heparin	Subcutaneous	5
Carvedilol	Tablets	5
Alfacalcidol	Tablets	5
Dobutamine	Intravenous	5
Aspirin	Tablets	4
Cefotaxime	Intravenous	4
Linezolid	Intravenous	4
Rifaximin	Tablets	4
Calcium gluconate	Intravenous	4
Imipenem+Cilastatin	Intravenous	3
Cefoperazone	Intravenous	3
Tramadol	Intravenous	3
Streptomycin	intramuscular	3
Methylprednisolone	Intravenous	3
Moxifloxacin	Intravenous	2
Clopidogrel+Aspirin	Tablets	2
Bisoprolol	Tablets	2
Atropine	Intravenous	2
Vancomycin	Intravenous	2
Metoclopramide	Intravenous	2
Baclofen	Tablets	2
Valproate sodium	Syrup	2
Calcitriol	Intravenous	2
Silymarin	Syrup	2

Iron sucrose	Intravenous	2
Epoetin alfa	Subcutaneous	2
Amoxicillin	Intravenous	2
Nimodipine	Tablets	1
Metoprolol	Tablets	1
Furosemide+Spironolactone	Tablets	1
Ranitidine	Tablets	1
Losartan	Tablets	1
Enalapril+Hydrochlorothiazide	Tablets	1
Carbamazepine	Tablets	1
Amikacin	Intravenous	1
Nitroglycerin	Tablets	1
Ketorolac	Intravenous	1
Spironolactone	Tablets	1
Levetiracetam	Tablets	1
Piracetam	Intravenous	1
Atorvastatin	Tablets	1
Clarithromycin	Tablets	1
Folic acid	Tablets	1
Captopril	Tablets	1
Domperidone	Tablets	1
Candesartan	Tablets	1
Methyldopa	Tablets	1
Rifmapin+Isoniazid+Pyrazinamide+Ethambutol	Tablets	1
Prochlorperazine	Tablets	1
Artemether+Lumefantrine	Intravenous	1
Fluconazole	Intravenous	1
Citalopram	Tablets	1
Potassium chloride	Tablets	1
Famotidine	Syrup	1
Piroxicam	Tablets	1
Dothiepin	Tablets	1
Azithromycin	Intravenous	1

Clindamycin	Tablets	1
Co-amoxiclav	Tablets	1
Ampicillin	Intravenous	1
Hydralazine	Intravenous	1

3.2.1.8 Indications

Secondary infection was the most prevalent indication in the MICU of LRH (311 cases of 1129) followed by stress ulcer (191 cases), asthma (105 cases), tetanus (62 cases), spasticity (52 cases), inflammation (29 cases), seizures (28 cases) and respiratory tract infections (27 cases), while the rest of the cases were contributed by other indications.

3.2.1.9 Drug class

A total of 34 drug classes were used in the MICU of LRH with antibacterial being the most prevalent drug class as shown in Table 3.48.

Table 3.48 Frequencies of Drug classes used in the MICU of LRH

Drug Class	Frequency
Antibacterial	436
Proton pump inhibitors	136
Bronchodilator	85
Corticosteroids	75
H2 receptor antagonists	56
Anticonvulsant	49
Anticoagulant	45
Skeletal muscle relaxant	29
Nutriceutical	26
Analgesic	25
Liver protectant	25
Antiviral	17
Antimalarial	13
Laxative	13
Antiemetic	11
Diuretic	9
Calcium channel blocker	9
Vasopressor	9
Antiplatelet	8
Beta blocker	8
ACE inhibitor	7
Hemostatic	7
HMG Co-A reductase inhibitor	6
Adrenergic agonist	6
Antianemic	3
Anxiolytic	2
ARBs	2
Cholinergic antagonist	2
Hematopoietic	2

Nitrates	1
Nootropic agent	1
Alpha adrenergic agonist	1
Antitubercular	1
Vasodilator	1

3.2.1.10 Dosing errors in the MICU of LRH

Of the total 1126 cases, 193 (17.1%) had subtherapeutic doses while 36 (3.2%) had overdoses as shown in Table 3.49 and Table 3.50 respectively.

Table 3.49 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Piperacillin + Tazobactam	Intravenous	86
Ranitidine	Intravenous	37
Metronidazole	Intravenous	24
Ipratropium	Nebules	10
Ceftriaxone	Intravenous	7
Enoxaparin	Subcutaneous	6
Meropenem	Intravenous	4
Amoxicillin	Intravenous	2
Baclofen	Tablets	2
Carvedilol	Tablets	2
Imipenem+Cilastatin	Intravenous	1
Ketorolac	Intravenous	1
Piracetam	Intravenous	1
Dexamethasone	Intravenous	1
Domperidone	Tablets	1
Citalopram	Tablets	1
Clindamycin	Tablets	1
Ramipril	Tablets	1
Nifedipine	Tablets	1
Nitroglycerin	Tablets	1
Methyl Dopa	Tablets	1
Beclomethasone	Nebules	1
Lactulose	Syrup	1

Table 3.50 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Dexamethasone	Intravenous	11
Lactulose	Syrup	6
Levofloxacin	Intravenous	4
Enoxaparin	Subcutaneous	3
Albuterol	Nebules	3
Beclomethasone	Nebules	2
Ceftriaxone	Intravenous	1
Tranexamic acid	Intravenous	1
Artemether+Lumefantrine	Intravenous	1
Diazepam	Intravenous	1
Citalopram	Tablets	1
Levetiracetam	Tablets	1
Heparin	Subcutaneous	1

3.2.2 Khyber Teaching Hospital (KTH)

3.2.2.1 General Patient Characteristics

In MICU of KTH, 210 patients were analyzed, 103 (49.0%) were males and 107 (51.0%) were females. The mean age of the population was 45.12 years and it ranged from 12 to 98 years. Of the total patients, 53.3% were between the age of 19 to 59 years, 33.8% were of 60 years and/or older and 12.9% were of 18 years and below. Mean duration of stay in the critical care unit was 5.67 ± (4.26) days, while the mean number of prescribed drugs were 5.70 ± (1.86) as shown in Table 3.51.

The top three leading causes of admission in the MICU or KTH were acute gastroenteritis, chronic obstructive pulmonary disease (COPD) and cerebrovascular accident (CVA) as shown in Figure 3.6.

Table 3.51 General Characteristics of Patients in MICU of KTH

Variables	**Frequency (%)**
Gender	
Male	103 (49.0%)
Female	107 (51.0%)
Age (years)	
Mean ± SD	45.12 (± 21.26)
Median	45
Range	12-98
≤ 18	27 (12.9%)
19-59	112 (53.3%)
≥ 60	71 (33.8%)
Drugs prescribed per patient	
Mean ± SD	5.70 ± (1.86)
Median	6
Range	2-11
≤ 4	57 (27.2%)
5-6	91 (43.3%)
≥ 7	62 (29.5%)
Stay in ICU (days)	
Mean ± SD	5.67 ± (4.26)
Median	4
Range	2-36
≤ 2	26 (12.4%)
3-5	82 (39.0%)
≥ 6	102 (48.6%)

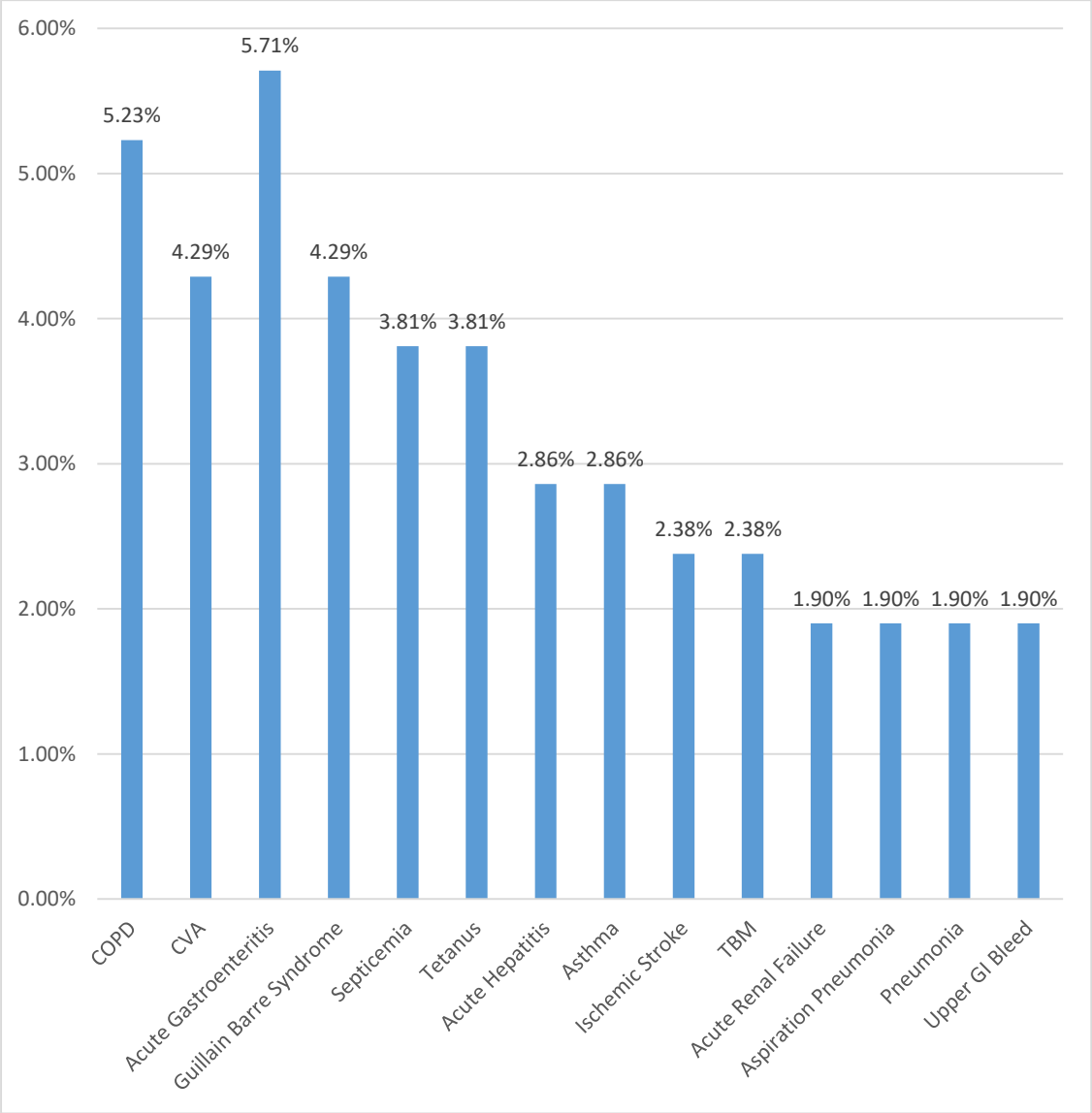

Figure 3.6 Causes of admission to MICU of KTH

3.2.2.2 Prevalence of Potential drug-drug interactions

The prevalence of PDDIs in patients of MICU of KTH was reported to be 46.7%. Of the total 210 patients, 22.4% patients had at least 1 PDDI, 9.5% patients had 2 PDDIs, 4.3% patients had 3 PDDIs, 1.9% patients each had 4,5,6,7 and 8 PDDIs and 1.0% patients had 10 PPDIs as shown in Table 3.52.

Table 3.52 Prevalence of PDDIs in MICU of KTH

NO. OF PDDIS	Frequency	Percentage %
1	47	22.4
2	20	9.5
3	9	4.3
4	4	1.9
5	4	1.9
6	4	1.9
7	4	1.9
8	4	1.9
10	2	1.0

3.2.2.3 Categories of PDDIs

Severity, documentation, onset, type and mechanism of interactions were the parameters used to classify the PDDIs reported in the MICU of KTH. A total of 96 interacting drug pairs were identified which caused 254 drug-drug interactions. According to severity 49.6% of the PDDIs were major, 44.5% were moderate and 4.3% were minor while 1.6% were contraindicated. Based on documentation of PDDIs, 13% were of excellent documentation, 33.5% were of good and 53.5% were of fair documentation. The onset of 9.9% PDDIs was rapid while 36.2% were of delayed and 53.9% were of unknown onset. According to type of interactions, 67.3% PDDIs were of pharmacokinetic nature and 26.4% PDDIs were of pharmacodynamic nature while 6.3% PDDIs were of unknown type. In terms of mechanism, synergism was involved in 24% PDDIs, antagonism was involved in 2.4% PDDIs, absorption contributed to

5.1% PDDIs, metabolism contributed for 55.5% PDDIs, elimination contributed in 5.9% PDDIs, combination of absorption and metabolism contributed in 0.8% PDDIs while 6.3% PDDIs were of unknown mechanisms as shown in Table 3.53.

Table 3.53 Categories of PDDIs in MICU of KTH

Variable	**Frequency (%)**
Severity of PDDIs	
Major	126 (49.6%)
Moderate	113 (44.5%)
Minor	11 (4.3%)
Contraindicated	4 (1.6%)
Documentation of PDDIs	
Excellent	33 (13.0%)
Good	85 (33.5%)
Fair	136 (53.5%)
Onset of PDDIs	
Rapid	25 (9.9%)
Delayed	92 (36.2%)
Unkonwn	137 (53.9%)
Type of Interaction	
Pharmacodynamic	171 (26.4%)
Pharmacokinetic	67 (67.3%)
Unknown	16 (6.3%)
Mechanism of Interaction	
Synergism	61 (24.0%)
Antagonism	6 (2.4%)
Absorption	13 (5.1%)
Metabolism	141 (55.5%)
Elimination	15 (5.9%)
Absorption/Metabolism	2 (0.8%)
Unknown	16 (6.3%)

3.2.2.4 Interacting Drug Pairs

In the MICU of KTH, 96 interacting drug pairs were identified causing 254 drug-drug interactions, of these interacting drug pairs, 12 were involved in 93 (36.6%) interactions of which 9 were major and 3 were moderate as shown in Table 3.54.

Table 3.54 Interacting drug pairs in the MICU of KTH

Interacting Pair	Frequency	Percentage
clarithromycin-dexamethasone	13	5.1%
carbamazepine-dexamethasone	11	4.3%
clarithromycin-metronidazole	10	3.9%
carbamazepine-metronidazole	10	3.9%
clopidogrel-omeprazole	9	3.5%
clopidogrel-enoxaparin	7	2.8%
ciprofloxacin-metronidazole	7	2.8%
carbamazepine-ranitidine	6	2.4%
dexamethasone-nimodipine	5	2.0%
aspirin-clopidogrel	5	2.0%
dexamethasone-rifampin	5	2.0%
metronidazole-octreotide	5	2.0%
pyrazinamide-rifampin	4	1.6%
aspirin-dexamethasone	4	1.6%
fluconazole-metronidazole	4	1.6%
carbamazepine-phenytoin	4	1.6%
amlodipine-dexamethasone	4	1.6%
fluconazole-lansoprazole	4	1.6%
dexamethasone-phenytoin	3	1.2%
aspirin-ranitidine	3	1.2%
acyclovir-valproate sodium	3	1.2%
amlodipine-clarithromycin	3	1.2%

atorvastatin-clopidogrel	3	1.2%
dexamethasone-moxifloxacin	3	1.2%
metronidazole-quinine	3	1.2%
carbamazepine-clarithromycin	3	1.2%
levofloxacin-metronidazole	3	1.2%
acyclovir-phenytoin	3	1.2%
carbamazepine-omeprazole	3	1.2%
phenytoin-ranitidine	3	1.2%
carbamazepine-nimodipine	3	1.2%
carbamazepine-valproate	3	1.2%
atorvastatin-clarithromycin	2	0.8%
clarithromycin-tramadol	2	0.8%
amlodipine-clopidogrel	2	0.8%
aspirin-bisoprolol	2	0.8%
digoxin-furosemide	2	0.8%
clarithromycin-valproate	2	0.8%
furosemide-lisinopril	2	0.8%
carbamazepine-clonazepam	2	0.8%
amiodarone-digoxin	2	0.8%
nimodipine-valproate	2	0.8%
clarithromycin-simvastatin	2	0.8%
ampicillin-omeprazole	2	0.8%
clarithromycin-fluticasone	2	0.8%
furosemide-propranolol	2	0.8%
magnesium sulfate-nifedipine	2	0.8%
diclofenac-heparin	2	0.8%
digoxin-omeprazole	2	0.8%
metronidazole-phenytoin	2	0.8%
valproic acid-isoniazid	2	0.8%
amiodarone-clopidogrel	2	0.8%
clopidogrel-heparin	2	0.8%

dexamethasone-fluconazole	2	0.8%
clarithromycin-salmeterol	2	0.8%
omeprazole-propranolol	2	0.8%
rifampin-valproic acid	2	0.8%
fluconazole-moxifloxacin	2	0.8%
rifampin-omeprazole	2	0.8%
ciprofloxacin-propranolol	2	0.8%
amiodarone-dexamethasone	2	0.8%
atorvastatin-carbamazepine	2	0.8%
clonazepam-phenytoin	2	0.8%
clarithromycin-phenytoin	1	0.4%
albuterol-bisoprolol	1	0.4%
aspirin-ramipril	1	0.4%
aspirin-enoxaparin	1	0.4%
albuterol-carvedilol	1	0.4%
losartan-spironolactone	1	0.4%
artemether/lumefantrine-dexamethasone	1	0.4%
ceftriaxone-cyclosporine	1	0.4%
erlotinib-omeprazole	1	0.4%
ciprofloxacin-sucralfate	1	0.4%
aspirin-atenolol	1	0.4%
clarithromycin-nimodipine	1	0.4%
amlodipine-aspirin	1	0.4%
dexamethasone-levofloxacin	1	0.4%
artemether/lumefantrine-metronidazole	1	0.4%
dexamethasone-nifedipine	1	0.4%
amikacin-furosemide	1	0.4%
aspirin-nifedipine	1	0.4%
amlodipine-atenolol	1	0.4%
cyclosporine-metronidazole	1	0.4%
paracetamol-isoniazid	1	0.4%

carbamazepine-quinine	1	0.4%
amlodipine-ciprofloxacin	1	0.4%
clopidogrel-nifedipine	1	0.4%
isoniazid-rifampin	1	0.4%
clarithromycin-lansoprazole	1	0.4%
artemether/lumefantrine-levofloxacin	1	0.4%
quinine-rifampin	1	0.4%
clarithromycin-rosuvastatin	1	0.4%
carbamazepine-rifampin	1	0.4%
bisoprolol-nifedipine	1	0.4%
phenytoin-valproate	1	0.4%
rifampin-valproate	1	0.4%

3.2.2.5 Clinical importance of PDDIs in MICU of KTH

Clinically significant PDDIs were identified using the predetermined criterion and analysis resulted in the identification of 46 interacting pairs which were of clinical significance 1 and 2. These 46 pairs contributed to 40.2% of the total potential drug-drug interactions (98 of 254), of which 17 were of clinically significance 1 while 29 were of clinical significance 2. These clinically significant PDDIs along with their potential outcomes are shown in Table 3.55.

Table 3.55 Clinically important interacting pairs and their potential outcomes in MICU of KTH

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Carbamazepine-clonazepam	1	2	May result in reduced plasma levels of clonazepam	198,199
Carbamazepine-nimodipine	1	3	Reduced nimodipine plasma concentrations and reduced nimodipine efficacy.	107
Aspirin-enoxaparin	1	1	Increased risk of bleeding.	200
Clopidogrel-omeprazole	1	9	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	105,106
Carbamazepine-quinine	1	1	Decreased quinine plasma concentrations and efficacy; increased carbamazepine exposure	201
Isoniazid-rifampin	1	1	Hepatotoxicity	202
Pyrazinamide-rifampin	1	4	Severe hepatic injury.	203
Carbamazepine-clarithromycin	1	3	May result in decreased exposure of clarithromycin; increased exposure of carbamazepine.	191
Quinine-rifampin	1	1	Decreased quinine exposure, plasma concentrations, and efficacy.	204
Erlotinib-omeprazole	1	1	Reduced absorption of erlotinib.	205

Amiodarone-digoxin	1	2	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[206]
Amlodipine-clopidogrel	1	2	Decreased antiplatelet effect and increased risk of thrombotic events.	[207]
Atorvastatin-clarithromycin	1	2	Increased atorvastatin exposure and an increased risk of myopathy or rhabdomyolysis.	[130,131]
Clopidogrel-nifedipine	1	1	Decreased antiplatelet effect and increased risk of thrombotic events.	[207,208]
Dexamethasone-nifedipine	1	1	May result in decreased nifedipine exposure.	[191]
Carbamazepine-phenytoin	1	4	Decreased phenytoin and/or carbamazepine concentrations.	[209]
Clarithromycin-phenytoin	1	1	Decreased clarithromycin plasma concentrations.	[126]
Furosemide-lisinopril	2	2	May result in postural hypotension (first dose).	[151]
Dexamethasone-rifampin	2	4	May result in decreased dexamethasone effectiveness	[120]
Aspirin-dexamethasone	2	4	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[142,115]
Dexamethasone-levofloxacin	2	1	Increased risk of tendon rupture.	[165]
Aspirin-bisoprolol	2	2	May result in decreased antihypertensive effect.	[124,125]
Aspirin-atenolol	2	1	May result in decreased antihypertensive effect.	[124,125]
Rifampin-valproic acid	2	1	May result in reduced valproate levels.	[126,28]

Carbamazepine-metronidazole	2	6	Increased carbamazepine serum concentrations and potential carbamazepine toxicity.	[196]
Bisoprolol-nifedipine	2	1	May result in hypotension and/or bradycardia	[197]
Amiodarone-clopidogrel	2	2	Ineffective inhibition of platelet aggregation.	[188]
Acyclovir-phenytoin	2	3	Decreased phenytoin plasma concentrations and potential increased seizure activity.	[195]
Acyclovir-valproate	2	3	Decreased valproic acid plasma concentrations and potential increased seizure activity.	[195]
Aspirin-nifedipine	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect	[143]
Atorvastatin-clopidogrel	2	3	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.	[210]
Carbamazepine-rifampin	2	1	Decreased carbamazepine exposure and possible loss of efficacy.	[28]
Carbamazepine-valproate	2	3	Increased serum levels of valproate.	[211]
Dexamethasone-moxifloxacin	2	3	Increased risk of tendon rupture.	[165]
Dexamethasone-phenytoin	2	3	Decreased dexamethasone effectiveness.	[108]
Carbamazepine-omeprazole	2	3	Increased risk of carbamazepine toxicity.	[212]

Digoxin-furosemide	2	2	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[213]
Digoxin-omeprazole	2	1	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[214]
Phenytoin-valproate	2	1	Altered valproate levels or altered phenytoin levels.	[215]
Amlodipine-atenolol	2	1	May result in hypotension and/or bradycardia.	[216]
Ciprofloxacin-sucralfate	2	1	May result in decreased ciprofloxacin effectiveness.	[217]
Cyclosporine-metronidazole	2	1	Increased risk of cyclosporine toxicity (nephrotoxicity, cholestasis, paresthesias).	[218]
Magnesium sulfate-nifedipine	2	1	May result in hypotension.	[219]
Nimodipine-valproate	2	2	May result in nimodipine toxicity (dizziness, headache, flushing, peripheral edema)	[107]
Paracetamol-isoniazid	2	1	May result in an increased risk of hepatotoxicity.	[220,221]
Amlodipine-aspirin	2	1	May result in an increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[141]

3.2.2.6 Association of PDDIs with other parameters in MICU of KTH

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 6 or more drugs (OR = 6.905; 95%CI = 3.555-13.410; p = 0.000) and with gender (OR = 0.517; 95%CI = 0.279-0.956; p = 0.035). An insignificant association was found between the presence of PDDIs and duration of stay of 4 or more days (OR = 0.896; 95%CI = 0.443-1.813; p = 0.760). The results are shown in Table 3.56.

Table 3.56 logistic regression analysis in MICU of KTH

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=98)	**Interactions absent (n=112)**		
Prescribed drugs				
< 6	24	76		
≥ 6	74	36	6.905 (3.555-13.410)	0.000
Duration of stay				
< 4	27	43		
≥ 4	71	69	0.896 (0.443-1.813)	0.760
Gender				
Male	56	47		
Female	42	65	0.517 (0.279-0.956)	0.035

3.2.2.7 Drugs used

A total of 127 drugs were prescribed in the MICU of KTH appearing 1193 times in all the medication charts as shown in Table 3.57.

Table 3.57 Frequencies of commonly used drugs in MICU of KTH

Drug Name	Dosage Form	Frequency
Ceftriaxone	Intravenous	125
Metronidazole	Intravenous	114
Omeprazole	Intravenous	100
Dexamethasone	Intravenous	75
Albuterol	Nebules	70
Ranitidine	Intravenous	61
Ipratropium	Intravenous	40
Furosemide	Nebules	23
Clarithromycin	Intravenous	23
Lactulose	Intravenous	23
Dimenhydrinate	Syrup	22
Heparin	Subcutaneous	19
Vitamin K	Intravenous	19
Cefoperazone+Sulbactam	Intravenous	18
Enoxaparin	Subcutaneous	17
Ciprofloxacin	Intravenous	15
Piperacillin+Tazobactam	Intravenous	14
Clopidogrel	Tablets	13
Carbamazepine	Tablets	13
Cefepime	Intravenous	12
Tramadol	Intravenous	12
Benzylpenicillin	Intravenous	11
Sucralfate	Syrup	11

Co-amoxiclav	Intravenous	10
Acyclovir	Intravenous	9
Esomeprazole	Intravenous	8
Losartan	Tablets	8
Valproate sodium	Intravenous	8
Nifedipine	Tablets	8
Clarithromycin	Tablets	8
Aspirin	Tablets	7
Isosorbide mononitrate	Tablets	7
Atorvastatin	Tablets	7
Beclomethasone	Nebules	7
Folic acid	Tablets	7
Rosuvastatin	Tablets	6
Diazepam	Intravenous	6
Amlodipine	Tablets	6
Metoclopramide	Intravenous	6
Lansoprazole	Intravenous	6
Paracetamol+Orphenadrine	Tablets	6
Hydrocortisone	Intravenous	6
Quinine	Intravenous	6
Domperidone	Tablets	6
Pantoprazole	Intravenous	6
Montelukast	Tablets	5
Nimodipine	Tablets	5
Octreotide	Subcutaneous	5
Potassium chloride	Tablets	5
Bisoprolol	Tablets	4
Phenytoin	Intravenous	4
Tranexamic acid	Intravenous	4
Dopamine	Intravenous	4
Ceftazidime	Intravenous	4
Fluconazole	Tablets	4
Carvedilol	Tablets	4

Gliclazide	Tablets	4
Dobutamine	Intravenous	4
Pyridoxine	Tablets	4
Doxycycline	Tablets	4
Pyrazinamide	Tablets	4
Clopidogrel+Aspirin	Tablets	3
Ranitidine	Tablets	3
Vancomycin	Intravenous	3
Propylthiouracil	Tablets	3
Amikacin	Intravenous	3
Spironolactone	Tablets	3
Propranolol	Tablets	3
Omeprazole	Tablets	3
Artemether+Lumefantrine	Tablets	3
Alfacalcidol	Tablets	3
Lisinopril	Tablets	3
Rifampin+Isoniazid	Tablets	3
Ciprofloxacin	Tablets	3
Digoxin	Tablets	2
Imipenem+Cilastatin	Intravenous	2
Ramipril	Tablets	2
Losartan+Hydrochlorothiazide	Tablets	2
Amiodarone	Tablets	2
Cefixime	Tablets	2
Meropenem	Intravenous	2
Ceftizoxime	Intravenous	2
Atenolol	Tablets	2
Ketorolac	Intravenous	2
Cefuroxime	Intravenous	2
Piracetam	Intravenous	2
Streptomycin	Intramuscular	2
Levofloxacin	Intravenous	2
Magnesium sulfate	Intravenous	2

Salmeterol+Fluticasone	Inhalation	2
Calcium gluconate	Intravenous	2
Moxifloxacin	Tablets	2
Domperidone	Syrup	2
Tizanidine	Tablets	2
Fluconazole	Intravenous	2
Diclofenac	Tablets	2
Clonazepam	Intravenous	2
Ampicillin-Cloxacillin	Tablets	2
Amoxicillin	Tablets	2
Simvastatin/Ezetimibe	Tablets	2
Perindopril+Amlodipine	Tablets	2
Metronidazole	Tablets	2
Diphenoxylate+Atropine	Tablets	2
Moxifloxacin	Intravenous	1
Valsartan+Hydrochlorothiazide	Tablets	1
Cefotaxime	Intravenous	1
Terlipressin	Intravenous	1
Cyclosporine	Tablets	1
Amlodipine+Valsartan	Tablets	1
Levofloxacin	Tablets	1
Rifaximin	Tablets	1
Clarithromycin	Syrup	1
Rifmapin+Isoniazid+Pyrazinamide+Ethambutol	Tablets	1
Valproate sodium	Syrup	1
Alprazolam	Tablets	1
Perindopril	Tablets	1
Sodium picosulfate	Syrup	1
Thyroxine	Tablets	1
Paracetamol	Tablets	1
Erlotinib	Tablets	1
Itopride	Tablets	1
Ethambutol	Tablets	1

Pyridostigmine	Tablets	1
Metronidazole	Syrup	1
Azathioprine	Tablets	1
Rifampin	Tablets	1
Doxofylline	Tablets	1

3.2.2.8 Indications

Secondary infection was the most prevalent indication in the MICU of KTH (273 cases of 1193) followed by stress ulcer (181 cases), asthma (122 cases), Respiratory tract infections (44 cases), inflammation (42 cases), hypertension and emesis (37 cases each), while the rest of the cases were contributed by other indications.

3.2.2.9 Drug class

A total of 47 drug classes were used in the MICU of KTH with antibacterial being the most prevalent drug class as shown in Table 3.58.

Table 3.58 Frequencies of Drug classes used in MICU of KTH

Drug Class	Frequency
Antibacterial	395
Proton pump inhibitors	124
Bronchodilator	115
Corticosteroids	88
H2 receptor antagonists	64
Anticoagulant	40
Antiemetic	36
Anticonvulsant	34
Nutriceutical	29
Diuretic	25
Analgesic	22
Calcium channel blocker	20
Antiplatelet	19
Liver protectant	17
HMG Co-A reductase inhibitor	15
Beta blocker	13
ARBs	11
Mucosal protective agents	11
Antitubercular	10
Antiviral	9
Antimalarial	9
ACE inhibitor	8
Nitrates	7
Antianemic	7
Laxative	7
Antifungal	6
Clotting activator	6
Hormone	5
Vasopressor	4

Antithyroid agent	4
Hemostatic	4
Sulfonyl ureas	4
Adrenergic agonist	4
Leukotriene receptor antagonist	3
Cardiac glycoside	2
Antiarrhythmic	2
Nootropic agent	2
Skeletal muscle relaxant	2
Antidiarrheal	2
Anxiolytic	1
Immune suppressant	1
Antipyretic	1
Anti neoplastic	1
Gastric prokinetic	1
Vasopressin	1
Cholinesterase inhibitor	1
Cytotoxic	1

3.2.2.10 Dosing errors in MICU of KTH

Out of the total 1190 cases, 107 (9.0%) had subtherapeutic doses while 51 (4.3%) had overdoses as shown in Table 3.59 and Table 3.60 respectively.

Table 3.59 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Ranitidine	Intravenous	45
Piperacillin + Tazobactam	Intravenous	11
Nimodipine	Tablets	5
Metronidazole	Intravenous	4
Enoxaparin	Subcutaneous	4
Hydrocortisone	Intravenous	3
Vancomycin	Intravenous	3
Co-amoxiclav	Intravenous	3
Isosorbide mononitrate	Tablets	3
Carvedilol	Tablets	3
Ceftriaxone	Intravenous	2
Cefuroxime	Intravenous	2
Fluconazole	Intravenous	2
Fluconazole	Tablets	2
Heparin	Subcutaneous	2
Octreotide	Subcutaneous	2
Ipratropium	Nebules	2
Albuterol	Nebules	2
Lactulose	Syrup	2
Alprazolam	Tablets	1
Ranitidine	Tablets	1
Phenytoin	Intravenous	1
Ketorolac	Intravenous	1
Dexamethasone	Intravenous	1

Table 3.60 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Dexamethasone	Intravenous	19
Sucralfate	Syrup	8
Enoxaparin	Subcutaneous	4
Omeprazole	Intravenous	4
Clonazepam	Intravenous	2
Lactulose	Syrup	2
Nifedipine	Tablets	2
Montelukast	Tablets	2
Rifampin+Isoniazid	Tablets	2
Losartan	Tablets	2
Clarithromycin	Intravenous	1
Albuterol	Nebules	1
Propylthiouracil	Tablets	1
Amlodipine	Tablets	1

3.2.3 Hayatabad Medical Complex (HMC)

3.2.3.1 General Patient Characteristics

In the MICU of HMC a total of 210 patients were analyzed, of which 99 (47.1%) were males and 111 (52.9%) were females. The mean age of the patients was 41.22 years and ranged from 1 to 91 years. Of the total patients, 63.3% patients were between the ages of 19 to 59 years, 10.5% were of 18 years and below, while 26.2% patients were of 60 years and above. Mean duration of stay in the critical care unit and mean number of prescribed drugs were 4.34 ± (2.99) days and 5.26 ± (1.80) drugs respectively as shown in Table 3.61.

The top three leading causes of admission in the MICU of HMC were tetanus, poisoning from different sources and aspiration pneumonia as shown in Figure 3.7.

Table 3.61 General Patient Characteristics in the MICU of HMC

Variables	**Frequency (%)**
Gender	
Male	99 (47.1%)
Female	111 (52.9%)
Age (years)	
Mean ± SD	41.22 (± 20.17)
Median	35
Range	1-99
≤ 18	22 (10.5%)
19-59	133 (63.3%)
≥ 60	55 (26.2%)
Drugs prescribed per patient	
Mean ± SD	5.26 ± (1.80)
Median	5
Range	2-11
≤ 4	65 (30.9%)
5-6	110 (52.4%)
≥ 7	35 (16.7%)
Stay in ICU (days)	
Mean ± SD	4.34 ± (2.99)
Median	4
Range	1-25
≤ 2	55 (26.2%)
3-5	84 (40.0%)
≥ 6	71 (33.8%)

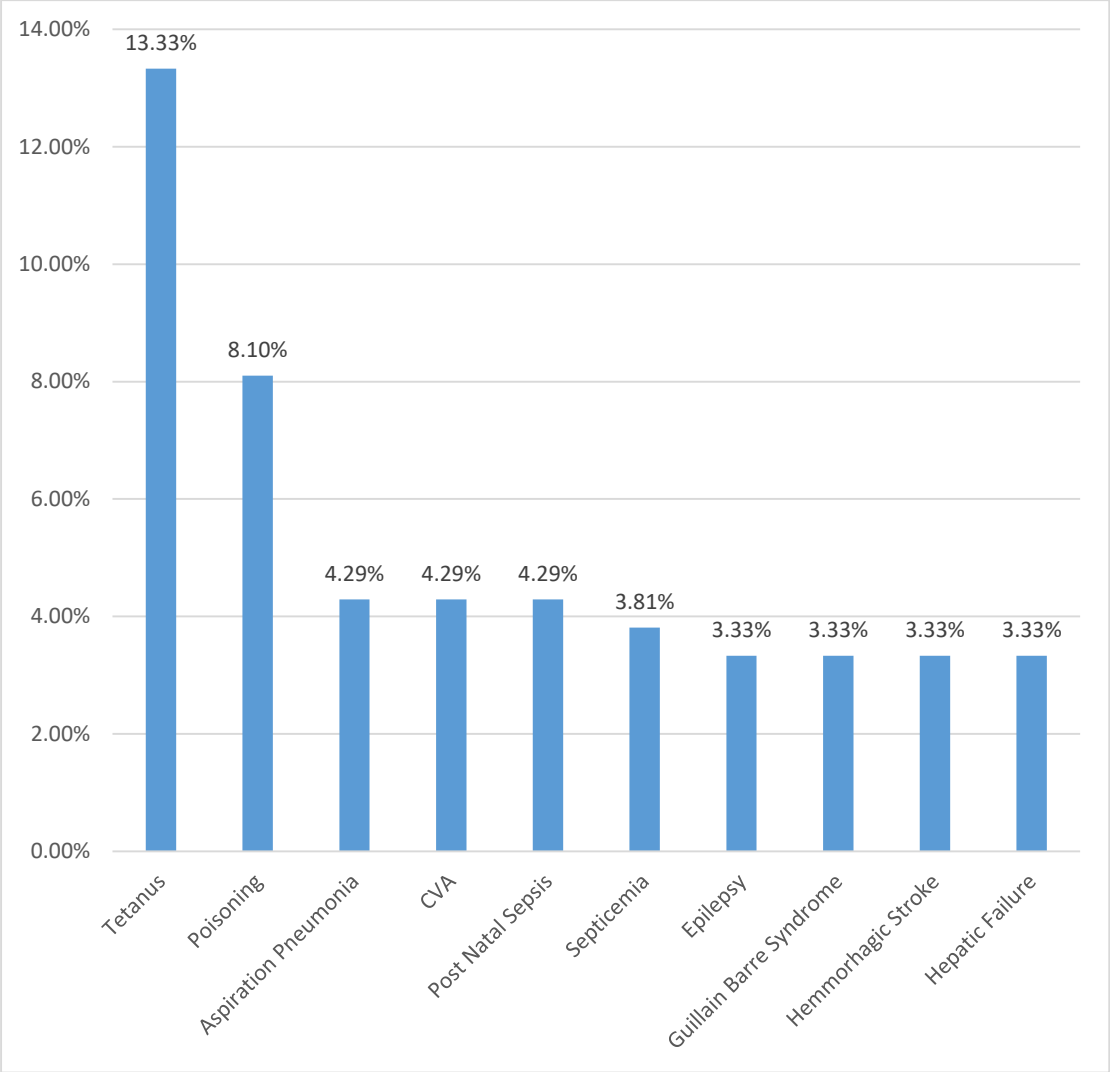

Figure 3.7 Causes of admission to MICU of HMC

3.2.3.2 Prevalence of Potential drug-drug interactions

A prevalence of 33.9% PDDIs was reported in the patients of MICU of HMC. Thirty eight patients encountered one PDDI, fifteen patients encountered two PDDIs, twelve patients encountered three PDDIs and one patient each encountered four and five PDDIs, while two patients encountered six PDDIs as shown in Table 3.62.

Table 3.62 Prevalence of PDDIs in the MICU of HMC

No. of PDDIs	Frequency	Percentage %
1	38	18.1
2	15	7.1
3	12	5.7
4	1	0.5
5	1	0.5
6	2	1.0

3.2.3.3 Categories of PDDIs

The PDDIs reported in the MICU of HMC were classified on the basis of severity, documentation, onset and clinical significance. The type and mechanisms of interactions were also identified. A total of 50 interacting drug pairs were identified which caused 125 drug-drug interactions. The severity of 51.2% PDDIs were major, 40.0% PDDIs were of moderate, 7.2% of the PDDIs were of minor severity and 1.6% PDDIs were contraindicated. The documentation of 48.8% PDDIs was fair, 39.2% PDDIs were of good documentation and 12.0% of the PDDIs were of excellent documentation. According to the onset of PDDIs, 14.4% were of rapid onset, 40.8% were of delayed onset while 44.8% were of unknown onset. In terms of type of PDDIs, pharmacokinetics and pharmacodynamics were involved in 58.4% and 37.6% PDDIs, while 4.0% PDDIs were of unknown type. In terms of mechanism, synergism contributed as the mechanism in 36.0% PDDIs, antagonism was involved in 1.6% PDDIs, absorption contributed to 7.2% PDDIs, metabolism contributed for 44.8% PDDIs, elimination contributed in 6.4% PDDIs, while 4% PDDIs were of unknown mechanisms. The results are shown in Table 3.63.

Table 3.63 Categories of PDDIs in the MICU of HMC

Variable	Frequency (%)
Severity of PDDIs	
Major	64 (51.2%)
Moderate	50 (40.0%)
Minor	9 (7.2%)
Contraindicated	2 (1.6%)
Documentation of PDDIs	
Excellent	15 (12.0%)
Good	49 (39.2%)
Fair	61 (48.8%)
Onset of PDDIs	
Rapid	18 (14.4%)
Delayed	51 (40.8%)
Unkonwn	56 (44.8%)
Type of Interaction	
Pharmacodynamic	47 (37.6%)
Pharmacokinetic	73 (58.4%)
Unknown	5 (4.0%)
Mechanism of Interaction	
Synergism	45 (36.0%)
Antagonism	2 (1.6%)
Absorption	9 (7.2%)
Metabolism	56 (44.8%)
Elimination	8 (6.4%)
Unknown	5 (4.0%)

3.2.3.4 Interacting Drug Pairs

In the MICU of HMC, 50 interacting drug pairs were identified causing 125 drug-drug interactions, of these interacting drug pairs, 7 were involved in 53 (42.4%) interactions of which 3 were major and 4 were moderate in severity as shown in Table 3.64.

Table 3.64 Interacting drug pairs in the MICU of HMC

Interacting Pair	Frequency	Percentage
clopidogrel-omeprazole	10	8.0%
acyclovir-valproate sodium	9	7.2%
clarithromycin-metronidazole	9	7.2%
metronidazole-tizanidine	7	5.6%
dexamethasone-rifampin	6	4.8%
valproic acid-isoniazid	6	4.8%
rifampin-valproic acid	6	4.8%
diazepam-omeprazole	5	4.0%
chlorpromazine-metronidazole	5	4.0%
nimodipine-valproate	4	3.2%
clarithromycin-dexamethasone	4	3.2%
clarithromycin-tramadol	3	2.4%
carbamazepine-omeprazole	3	2.4%
hydrocortisone-moxifloxacin	2	1.6%
aspirin-clopidogrel	2	1.6%
aspirin-enoxaparin	2	1.6%
clopidogrel-enoxaparin	2	1.6%
clopidogrel-fondaparinux	2	1.6%
aspirin-fondaparinux	2	1.6%
piperacillin/tazobactam+streptomycin	2	1.6%
amikacin-furosemide	2	1.6%
clopidogrel-heparin	2	1.6%

azithromycin-quinine	2	1.6%
amikacin-piperacillin	2	1.6%
dexamethasone-nimodipine	1	0.8%
aspirin-ramipril	1	0.8%
aspirin-nitroglycerin	1	0.8%
artemether/lumefantrine-dexamethasone	1	0.8%
diazepam-phenytoin	1	0.8%
clarithromycin-valproate	1	0.8%
citalopram-omeprazole	1	0.8%
clarithromycin-nifedipine	1	0.8%
aspirin-metoprolol	1	0.8%
fluconazole-cotrimoxazole	1	0.8%
metronidazole-quinine	1	0.8%
dexamethasone-nifedipine	1	0.8%
aspirin-dexamethasone	1	0.8%
artemether/lumefantrine-rifampin	1	.8%
metronidazole-phenytoin	1	0.8%
enalapril-spironolactone	1	0.8%
azithromycin-chlorpromazine	1	0.8%
metoprolol-nifedipine	1	0.8%
ciprofloxacin-dexamethasone	1	0.8%
acyclovir-valproic acid	1	0.8%
enalapril-furosemide	1	0.8%
clarithromycin-chlorpromazine	1	0.8%
azithromycin-metronidazole	1	0.8%
metoprolol-ranitidine	1	0.8%
clarithromycin-diazepam	1	0.8%
rifampin-omeprazole	1	0.8%

3.2.3.5 Clinical importance of PDDIs in the MICU of HMC

Analysis of the drug interaction pairs for clinical significance yielded 21 pairs having a clinical significance 1 or 2. These pairs contributed to 40.0% of the total PDDIs (50 of 125) of which 5 were of clinically significance 1 while 14 were of clinical significance 2 and 2 pairs were contraindicated (CI). The clinically significant drug interaction pairs along with their potential outcomes are shown in Table 3.65.

Table 3.65 Clinically important interacting pairs and their potential outcomes in MICU of HMC

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Artemether/lumefantrine-dexamethasone	CI	1	Efficacy of the antimalarial may be lost when used in combination with dexamethasone.	[79]
Artemether/lumefantrine-rifampin	CI	1	Efficacy of the antimalarial may be lost when used in combination with rifampin.	[79]
Aspirin-enoxaparin	1	2	Increased risk of bleeding.	[105,106]
Dexamethasone-nifedipine	1	1	May result in decreased nifedipine exposure.	[191]
Clopidogrel-omeprazole	1	10	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	[136,137]
Clarithromycin-nifedipine	1	1	May result in increased nifedipine plasma concentrations	[119]
Enalapril-spironolactone	1	1	May result in hyperkalemia.	[189,190]
Dexamethasone-rifampin	2	6	May result in decreased dexamethasone effectiveness	[120]
Aspirin-dexamethasone	2	1	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[142,115]
Ciprofloxacin-dexamethasone	2	1	Increased risk of tendon rupture.	[165]
Aspirin-metoprolol	2	2	May result in decreased antihypertensive effect.	[124,125]

Aspirin-nitroglycerin	2	1	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	[128]
Rifampin-valproic acid	2	6	May result in reduced valproate levels.	[126,28]
Acyclovir-valproate	2	3	Decreased valproic acid plasma concentrations and potential increased seizure activity.	
Carbamazepine-omeprazole	2	3	Increased risk of carbamazepine toxicity.	[195] [212]
Nimodipine-valproate	2	4	May result in nimodipine toxicity (dizziness, headache, flushing, peripheral edema)	[107]
Enalapril-furosemide	2	1	May result in postural hypotension (first dose).	[151]
Hydrocortisone-moxifloxacin	2	2	Increased risk of tendon rupture.	[165]
Clarithromycin-diazepam	2	1	May result in increased benzodiazepine toxicity (CNS depression, ataxia, lethargy).	[193]
Metoprolol-nifedipine	2	1	May result in hypotension and/or bradycardia.	[197]
Diazepam-phenytoin	2	1	May result in alterations in serum phenytoin concentrations.	[222]

3.2.3.6 Association of PDDIs with other parameters in the MICU of HMC

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 5 or more drugs (OR = 4.527; 95%CI = 2.069-9.906; p = 0.000). An insignificant association was found between the presence of PDDIs and duration of stay of 4 or more days (OR = 0.719; 95%CI = 0.393-1.315; p = 0.284), and with gender (OR = 1.044; 95%CI = 0.572-1.906; p = 0.889). The results are shown in Table 3.66.

Table 3.66 logistic regression analysis in the MICU of HMC

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=69)	**Interactions absent (n=141)**		
Prescribed drugs				
< 5	9	56		
≥ 5	60	85	4.527 (2.069-9.906)	0.000
Duration of stay				
< 4	34	61		
≥ 4	35	80	0.719 (0.393-1.315)	0.284
Gender				
Male	33	66		
Female	36	75	1.044 (0.572-1.906)	0.889

3.2.3.7 Drugs used

A total of 109 drugs were prescribed in the MICU of HMC appearing 1101 times in all the medication charts as shown in Table 3.67.

Table 3.67 Frequencies of commonly used drugs in the MICU of HMC

Drug name	Dosage form	Frequency
Omeprazole	Intravenous	115
Metronidazole	Intravenous	107
Ceftriaxone	Intravenous	63
Piperacillin + tazobactam	Intravenous	56
Enoxaparin	Subcutaneous	55
Dexamethasone	Intravenous	49
Albuterol	Nebules	39
Lactulose	Syrup	35
Cefoperazone + sulbactam	Intravenous	34
Valproate sodium	Intravenous	31
Ranitidine	Intravenous	29
Vitamin k	Intravenous	26
Ipratropium	Nebules	25
Clarithromycin	Intravenous	24
Benzylpenicillin	Intravenous	23
Beclomethasone	Nebules	17
Acyclovir	Intravenous	16
Dopamine	Intravenous	16
Co-amoxiclav	Intravenous	14
Vancomycin	Intravenous	14
Dobutamine	Intravenous	13
Cefotaxime	Intravenous	12
Rosuvastatin	Tablets	11
Diazepam	Intravenous	11
Baclofen	Tablets	11

Clopidogrel	Tablets	10
Tizanidine	Tablets	10
Esomeprazole	Intravenous	8
Dimenhydrinate	Intravenous	8
Chlorpromazine	Tablets	8
Furosemide	Intravenous	7
Fondaparinux	Subcutaneous	7
Atropine	Intravenous	7
Sucralfate	Syrup	7
Diazepam	Tablets	7
Imipenem+cilastatin	Intravenous	6
Linezolid	Intravenous	6
Meropenem	Intravenous	6
Levetiracetam	Tablets	6
Quinine	Intravenous	6
Rifmapin+isoniazid+pyrazinamide+ethambutol	Tablets	6
Moxifloxacin	Intravenous	5
Nimodipine	Tablets	5
Tranexamic acid	Intravenous	5
Tramadol	Intravenous	5
Metoclopramide	Intravenous	5
Cefepime	Intravenous	4
Terlipressin	Intravenous	4
Amlodipine	Tablets	4
Pyridoxine	Tablets	4
Carbamazepine	Tablets	3
Amikacin	Intravenous	3
Nifedipine	Tablets	3
Atorvastatin	Tablets	3
Clarithromycin	Tablets	3
Hydrocortisone	Intravenous	3
Alfacalcidol	Tablets	3
Calcium gluconate	Intravenous	3

Lisinopril+hydrochlorothiazide	Tablets	3
Azithromycin	Intravenous	3
Aspirin	Tablets	2
Ciprofloxacin	Intravenous	2
Clopidogrel+aspirin	Tablets	2
Bisoprolol	Tablets	2
Metoprolol	Tablets	2
Ramipril	Tablets	2
Losartan	Tablets	2
Isosorbide mononitrate	Tablets	2
Heparin	Subcutaneous	2
Ketorolac	Intravenous	2
Rifaximin	Tablets	2
Paracetamol+orphenadrine	Tablets	2
Streptomycin	Intramuscular	2
Carvedilol	Tablets	2
Octreotide	Subcutaneous	2
Potassium chloride	Tablets	2
Paracetamol	Intravenous	2
Codergocrine	Tablets	2
Orphenadrine+paracetamol	Tablets	2
Acetazolamide	Tablets	2
Phenytoin	Intravenous	1
Furosemide+spironolactone	Tablets	1
Ranitidine	Tablets	1
Enalapril+hydrochlorothiazide	Tablets	1
Propylthiouracil	Tablets	1
Nitroglycerin	Tablets	1
Spironolactone	Tablets	1
Piracetam	Intravenous	1
Fluconazole	Tablets	1
Folic acid	Tablets	1
Candesartan	Tablets	1

Magnesium sulfate	Intravenous	1
Moxifloxacin	Tablets	1
Artemether+lumefantrine	Intravenous	1
Bamifylline	Tablets	1
Citalopram	Tablets	1
Valproate sodium	Tablets	1
Methylprednisolone	Intravenous	1
Thyroxine	Tablets	1
Dothiepin	Tablets	1
Ethambutol	Tablets	1
Chlorpheniramine	Intravenous	1
Filgrastim	Intravenous	1
Ampicillin	Intravenous	1
Atracurium	Intravenous	1
Procyclidine	Tablets	1
Amoxicillin	Tablets	1
Propofol	Intravenous	1
Sulfamethoxazole+trimethoprim	Tablets	1

3.2.3.8 Indications

Secondary infection was the most prevalent indication in the MICU of HMC (274 cases of 1101) followed by stress ulcer (149 cases), asthma (78 cases), seizures (48 cases), tetanus (44 cases), deep vein thrombosis (42 cases), spasticity (34 cases) and shock (29 cases), while the rest of the cases were contributed by other indications.

3.2.3.9 Drug class

A total of 44 drug classes were used in the MICU of HMC with antibacterial being the most prevalent drug class as shown in Table 3.68.

Table 3.68 Frequencies of Drug classes used in the MICU of HMC

Drug Class	Frequency
Antibacterial	392
Proton pump inhibitors	123
Corticosteroids	70
Anticoagulant	67
Bronchodilator	65
Anticonvulsant	61
Nutriceutical	35
Vasopressor	31
H2 receptor antagonist	30
Analgesic	22
Liver protectant	20
Antiviral	15
HMG Co-A reductase inhibitor	14
Antiemetic	13
Laxative	13
Calcium channel blocker	12
Antiplatelet	11
Diuretic	10
Skeletal muscle relaxant	10
Antipsychotic	8
Cholinergic antagonist	7
Antimalarial	7
Mucosal protective agents	7
Antitubercular	7
Beta blocker	6
Ace inhibitor	6
Clotting activator	5
ARBs	3
Hemostatic	3

Nitrates	3
Anxiolytic	2
Antithyroid agent	2
Hormone	2
Antipyretic	2
Ergot alkaloid	2
Adrenergic agonist	2
Antiplasminic agent	2
Antifungal	1
H1 receptor antagonist	1
Antiparkinsonian	1
Hematopoietic	1
Musculoskeletal agent	1
Sedative	1
Carbonic anhydrase inhibitor	1

3.2.3.10 Dosing errors in the MICU of HMC

Out of the total 1093 cases, 121 (11.1%) had subtherapeutic doses while 46 (4.2%) had overdoses as shown in Table 3.69 and Table 3.70 respectively.

Table 3.69 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Piperacillin + Tazobactam	Intravenous	49
Ranitidine	Intravenous	18
Metronidazole	Intravenous	16
Valproate sodium	Intravenous	4
Dexamethasone	Intravenous	4
Enoxaparin	Subcutaneous	4
Nimodipine	Tablets	4
Co-amoxiclav	Intravenous	3
Ipratropium	Nebules	3
Meropenem	Intravenous	2
Cefepime	Intravenous	2
Ranitidine	Tablets	1
Citalopram	Tablets	1
Nitroglycerin	Tablets	1
Ceftriaxone	Intravenous	1
Cefotaxime	Intravenous	1
Carvedilol	Tablets	1
Vancomycin	Intravenous	1
Hydrocortisone	Intravenous	1
Piracetam	Intravenous	1
Baclofen	Tablets	1
Ramipril	Tablets	1
Artemether+Lumerfantrine	Intravenous	1

Table 3.70 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Dexamethasone	Intravenous	13
Lactulose	Syrup	7
Sucralfate	Syrup	7
Enoxaparin	Subcutaneous	5
Omeprazole	Intravenous	3
Levetiracteam	Tablets	3
Albuterol	Nebules	2
Beclomethasone	Nebules	2
Acetazolamide	Tablets	2
Diazepam	Intravenous	1
Tizanidine	Tablets	1

3.2.4 Northwest General Hospital and Research Center (NWGH & RC)

3.2.4.1 General Patient Characteristics

A total of 200 patients were analyzed in the MICU of NWGH & RC, of which 110 (55.0%) were males and 90 (45.0%) were females. The mean age of the population was 59.59 years and it ranged from 1 to 90 years Of the total patients, 43.5% were between the age of 19 to 59 years, 52.5% were of 60 years and/or above and 4% were of 18 years and below. Mean duration of stay in the critical care unit was 5.76 ± (3.62) days, while the mean number of prescribed drugs were 5.88 ± (2.17) as shown in Table 3.71.

The top three leading causes of admission in the MICU or NWGH & RC were chronic renal failure, COPD and CVA as shown in Figure 3.8.

Table 3.71 General Characteristics of Patients in MICU of NWGH& RC

Variables	**Frequency (%)**
Gender	
Male	110 (55.0%)
Female	90 (45.0%)
Age (years)	
Mean ± SD	59.59 (± 19.79)
Median	60
Range	1-90
≤ 18	8 (4.0%)
19-59	87 (43.5%)
≥ 60	105 (52.5%)
Drugs prescribed per patient	
Mean ± SD	5.88 ± (2.17)
Median	6
Range	2-13
≤ 4	54 (27.0%)
5-6	71 (35.5%)
≥ 7	75 (37.5%)
Stay in ICU (days)	
Mean ± SD	5.76 ± (3.62)
Median	5
Range	1-30
≤ 2	25 (12.5%)
3-5	66 (33.0%)
≥ 6	109 (54.5%)

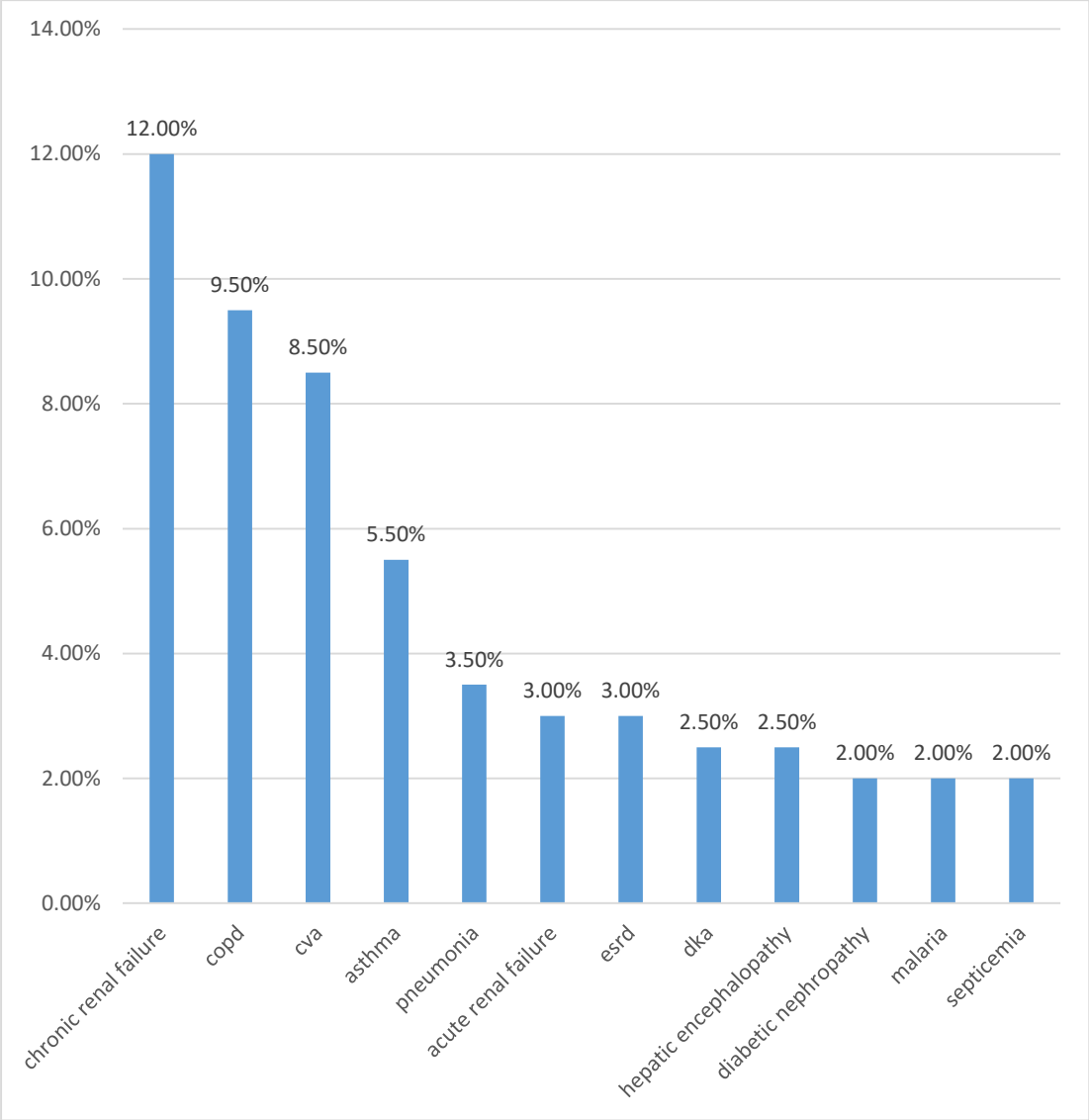

Figure 3.8 Causes of admission to MICU of NWGH & RC

3.2.4.2 Prevalence of Potential drug-drug interactions

The prevalence of PDDIs in patients of MICU of NWGH & RC was reported to be 39.5%. Of the total 200 patients, 21.5% patients had at least 1 PDDI, 6.0% patients had 2 PDDIs, 6.5% patients had 3 PDDIs, 1% patients each had 4,6 and 8 PDDIs, 1.5% patients had 5 PDDIs and 0.5% patients each had 12 and 14 PPDIs as shown in Table 3.72.

Table 3.72 Prevalence of PDDIs in MICU of NWGH& RC

NO. OF PDDIS	Frequency	Percentage %
1	43	21.5
2	12	6.0
3	13	6.5
4	2	1.0
5	3	1.5
6	2	1.0
8	2	1.0
12	1	0.5
14	1	0.5

3.2.4.3 Categories of PDDIs

Severity, documentation, onset, type and mechanism of interactions were the parameters used to classify the PDDIs reported in the MICU of NWGH & RC. A total of 84 interacting drug pairs were identified which caused 183 drug-drug interactions. According to severity 30.6% of the PDDIs were major, 61.2% were moderate and 8.2% were minor. Based on documentation of PDDIs, 32.2% were of excellent documentation, 38.3% were of good and 29.5% were of fair documentation. The onset of 13.6% PDDIs was rapid while 49.2% were of delayed onset and 37.2% were of unknown onset. According to type of interactions, 34.4% PDDIs were of pharmacokinetic nature and 41.5% PDDIs were of pharmacodynamic nature while 24.1% PDDIs were of unknown type. In terms of mechanism, synergism contributed as the mechanism in 31.7% PDDIs, antagonism was involved in 9.8% PDDIs, absorption

contributed to 6.6% PDDIs, metabolism contributed for 22.4% PDDIs, elimination contributed in 5.5% PDDIs while 24% PDDIs were of unknown mechanisms as shown in Table 3.73.

Table 3.73 Categories of PDDIs in MICU of NWGH& RC

Variable	**Frequency (%)**
Severity of PDDIs	
Major	56 (30.6%)
Moderate	112 (61.2%)
Minor	15 (8.2%)
Documentation of PDDIs	
Excellent	59 (32.2%)
Good	70 (38.3%)
Fair	54 (29.5%)
Onset of PDDIs	
Rapid	25 (13.6%)
Delayed	90 (49.2%)
Unkonwn	68 (37.2%)
Type of Interaction	
Pharmacodynamic	76 (41.5%)
Pharmacokinetic	63 (34.4%)
Unknown	44 (24.1%)
Mechanism of Interaction	
Synergism	58 (31.7%)
Antagonism	18 (9.8%)
Absorption	12 (6.6%)
Metabolism	41 (22.4%)
Elimination	10 (5.5%)
Unknown	44 (24.0%)

3.2.4.4 Interacting Drug Pairs

In the MICU of NWGH & RC, 84 interacting drug pairs were identified causing 183 drug-drug interactions, of these interacting drug pairs, 5 were involved in 62 (33.9%) interactions of which 2 were major, 2 were moderate and 1 was minor as shown in Table 3.74.

Table 3.74 Interacting drug pairs in MICU of NWGH& RC

Interacting Pair	Frequency	Percentage
hydrocortisone-moxifloxacin	32	17.5%
aspirin-clopidogrel	9	4.9%
aspirin-ranitidine	8	4.4%
aspirin-enoxaparin	7	3.8%
omeprazole-phenytoin	6	3.3%
aspirin-furosemide	4	2.2%
clopidogrel-enoxaparin	4	2.2%
clopidogrel-omeprazole	4	2.2%
midazolam-omeprazole	4	2.2%
furosemide-hydrocortisone	4	2.2%
aspirin-amlodipine	3	1.6%
losartan-spironolactone	3	1.6%
clopidogrel-esomeprazole	3	1.6%
acyclovir-phenytoin	3	1.6%
aspirin-carvedilol	3	1.6%
carvedilol-digoxin	3	1.6%
clarithromycin-moxifloxacin	2	1.1%
aspirin-perindopril	2	1.1%
amlodipine-clopidogrel	2	1.1%
albuterol-carvedilol	2	1.1%
digoxin-furosemide	2	1.1%
furosemide-lisinopril	2	1.1%

aspirin-lisinopril	2	1.1%
clarithromycin-digoxin	2	1.1%
amlodipine-aspirin	2	1.1%
aspirin-dexamethasone	2	1.1%
aspirin-nimodipine	2	1.1%
metronidazole-phenytoin	2	1.1%
albuterol-digoxin	2	1.1%
aspirin-diltiazem	2	1.1%
clopidogrel-diltiazem	2	1.1%
dexamethasone-nimodipine	1	0.5%
ketorolac-phenytoin	1	0.5%
dexamethasone-phenytoin	1	0.5%
atracurium-dexamethasone	1	0.5%
phenytoin-metronidazole	1	0.5%
albuterol-bisoprolol	1	0.5%
carbamazepine-hydrocortisone	1	0.5%
rifampin-isoniazid	1	0.5%
albuterol-nebivolol	1	0.5%
furosemide-metolazone	1	0.5%
aspirin-bisoprolol	1	0.5%
aspirin-nitroglycerin	1	0.5%
dexamethasone-rifampin	1	0.5%
pyrazinamide-rifampin	1	0.5%
meropenem-valproate	1	0.5%
imipenem-valproate sodium	1	0.5%
albuterol-linezolid	1	0.5%
aspirin-candesartan	1	0.5%
aspirin-valsartan	1	0.5%
amlodipine-bisoprolol	1	0.5%
aspirin-hydrochlorothiazide	1	0.5%
aspirin-metoprolol	1	0.5%

amlodipine-carvedilol	1	0.5%
albuterol-metoprolol	1	0.5%
clarithromycin-dexamethasone	1	0.5%
clarithromycin-metronidazole	1	0.5%
metoclopramide-tramadol	1	0.5%
metronidazole-ondansetron	1	0.5%
aspirin-nifedipine	1	0.5%
moxifloxacin-rifampin	1	0.5%
propranolol-verapamil	1	0.5%
amlodipine-nebivolol	1	0.5%
calcitriol-metolazone	1	0.5%
aspirin-spironolactone	1	0.5%
omeprazole-propranolol	1	0.5%
phenytoin-ranitidine	1	0.5%
rifampin-esomeprazole	1	0.5%
aspirin-irbesartan	1	0.5%
potassium chloride-valsartan	1	0.5%
ferrous suphate-pantoprazole	1	0.5%
clopidogrel-nifedipine	1	0.5%
levothyroxine-omeprazole	1	0.5%
carbamazepine-ranitidine	1	0.5%
aspirin-levofloxacin	1	0.5%
aspirin-hydrocortisone	1	0.5%
perindopril-spironolactone	1	0.5%
carvedilol-dobutamine	1	0.5%
diltiazem-metoprolol	1	0.5%
carvedilol-nifedipine	1	0.5%
amlodipine-diltiazem	1	0.5%
amlodipine-metoprolol	1	0.5%
diltiazem-ranitidine	1	0.5%
furosemide-perindopril	1	0.5%

3.2.4.5 Clinical importance of PDDIs in MICU of NWGH& RC

Clinically significant PDDIs were identified using the predetermined criterion and analysis resulted in the identification of 50 interacting pairs which were of clinical significance 1 and 2. These 50 pairs contributed to 61.2% of the total potential drug-drug interactions (112 of 183), of which 16 were of clinically significance 1 while 34 were of clinical significance 2. These clinically significant PDDIs along with their potential outcomes are shown in Table 3.75.

Table 3.75 Clinically important interacting pairs and their potential outcomes in the MICU of NWGH & RC

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Aspirin-enoxaparin	1	7	Increased risk of bleeding.	105,106
Clopidogrel-omeprazole	1	4	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	136,137
Perindopril-spironolactone	1	1	May result in hyperkalemia.	189,190
Isoniazid-rifampin	1	1	Hepatotoxicity	202
Pyrazinamide-rifampin	1	1	Severe hepatic injury.	203
Clopidogrel-nifedipine	1	1	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Meropenem-valproate	1	1	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	96,97,98,99
Clopidogrel-esomeprazole	1	3	May result in reduced plasma concentrations of clopidogrel active metabolite.	138,139
Albuterol-linezolid	1	1	Increased risk of cardiovascular adverse effects	116,117
Imipenem-valproate	1	1	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	96,97,98,99
Amlodipine-clopidogrel	1	2	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208

Clarithromycin-digoxin	1	2	May result in digoxin toxicity (nausea, vomiting, arrhythmias).	[223,224]
Clopidogrel-diltiazem	1	2	May result in increased diltiazem exposure.	[225]
Diltiazem-metoprolol	1	1	Increased risk of hypotension, bradycardia, AV conduction disturbances.	[226]
Furosemide-metolazone	1	1	May result in increased risk of electrolyte and fluid imbalance.	[227]
Propranolol-verapamil	1	1	May result in hypotension, bradycardia.	[228]
Dexamethasone-rifampin	2	1	May result in decreased dexamethasone effectiveness	[120]
Aspirin-dexamethasone	2	2	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[142,115]
Aspirin-metoprolol	2	1	May result in decreased antihypertensive effect.	[165]
Aspirin-nitroglycerin	2	1	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	[124,125]
Furosemide-lisinopril	2	2	May result in postural hypotension (first dose).	[151]
Furosemide-perindopril	2	1	May result in postural hypotension (first dose).	[151]
Dexamethasone-phenytoin	2	1	Decreased dexamethasone effectiveness.	[107]
Aspirin-furosemide	2	4	May result in decreased diuretic and antihypertensive efficacy.	[121,122]

Aspirin-spironolactone	2	1	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.	[123]
Aspirin-carvedilol	2	3	May result in decreased antihypertensive effect.	[124,125]
Aspirin-irbesartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-valsartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-candesartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-bisoprolol	2	1	May result in decreased antihypertensive effect.	[124,125]
Aspirin-amlodipine	2	5	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[141]
Aspirin-nimodipine	2	2	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[143,144]
Aspirin-nifedipine	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[143,144]
Aspirin-hydrochlorothiazide	2	1	Decreased diuretic and antihypertensive efficacy.	[145]
Amlodipine-bisoprolol	2	1	May result in hypotension and/or bradycardia.	[152,153]
Amlodipine-metoprolol	2	1	May result in hypotension and/or bradycardia.	[152,153]

Atracurium-dexamethasone	2	1	Decreased atracurium effectiveness; prolonged muscle weakness and myopathy.	[149,150]
Hydrocortisone-moxifloxacin	2	32	Increased risk of tendon rupture.	[165]
Levothyroxine-omeprazole	2	1	May result in increased TSH levels.	[173,174]
Acyclovir-phenytoin	2	3	Decreased phenytoin plasma concentrations and potential increased seizure activity.	[195]
Digoxin-furosemide	2	2	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[213]
Amlodipine-carvedilol	2	1	May result in hypotension and/or bradycardia.	[216]
Amlodipine-diltiazem	2	1	May result in increased amlodipine concentrations.	[229]
Amlodipine-nebivolol	2	1	May result in hypotension and/or bradycardia.	[216]
Aspirin-diltiazem	2	2	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Aspirin-lisinopril	2	2	May result in decreased lisinopril effectiveness.	[230]
Carvedilol-dobutamine	2	1	May result in decreased dobutamine efficacy.	[231]
Carvedilol-digoxin	2	1	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[232]
Carvedilol-nifedipine	2	1	May result in hypotension and/or bradycardia.	[216]
Moxifloxacin-rifampin	2	1	Decreased moxifloxacin exposure	[233]

3.2.4.6 Association of PDDIs with other parameters in MICU of NWGH& RC

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 6 or more drugs (OR = 4.868; 95%CI = 2.532-9.359; p = 0.000). An insignificant association was found between the presence of PDDIs and duration of stay of 5 or more days (OR = 1.593; 95%CI = 0.856-2.966; p = 0.142), and with gender (OR = 1.793; 95%CI = 0.927-3.264; p = 0.085). The results are shown in Table 3.76.

Table 3.76 logistic regression analysis in MICU of NWGH& RC

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=79)	**Interactions absent (n=121)**		
Prescribed drugs				
< 6	19	72		
≥ 6	60	49	4.868 (2.532-9.359)	0.000
Duration of stay				
< 5	29	62		
≥ 5	50	59	1.593 (0.856-2.966)	0.142
Gender				
Male	40	70		
Female	39	51	1.793 (0.927-3.264)	0.085

3.2.4.7 Drugs used

A total of 125 drugs were prescribed in the MICU of NWGH & RC appearing 1172 times in all the medication charts as shown in Table 3.77.

Table 3.77 Frequencies of commonly used drugs in MICU of NWGH& RC

Drug Name	Dosage Form	Frequency
Ceftriaxone	Intravenous	88
Albuterol	Nebules	74
Omeprazole	Intravenous	63
Beclomethasone	Nebules	53
Moxifloxacin	Intravenous	52
Ipratropium	Nebules	49
Esomeprazole	Intravenous	47
Ranitidine	Intravenous	47
Enoxaparin	subcutaneous	47
Hydrocortisone	Intravenous	47
Piperacillin + tazobactam	Intravenous	39
Metronidazole	Intravenous	38
Meropenem	Intravenous	33
Lactulose	Syrup	29
Alfacalcidol	Tablet	18
Vitamin K	Intravenous	18
Dexamethasone	Intravenous	17
Cefoperazone+sulbactam	Intravenous	16
Rosuvastatin	Tablet	16
Furosemide	Intravenous	16
Aspirin	Tablet	15
Imipenem+cilastatin	Intravenous	15
Amlodipine	Tablet	15
Dimenhydrinate	Intravenous	13
Dopamine	Intravenous	13
Co-amoxiclav	Intravenous	11
Metoclopramide	Intravenous	11

Acyclovir	Intravenous	10
Folic acid	Tablet	10
Norepinephrine	Intravenous	10
Clopidogrel+aspirin	Tablet	9
Tramadol	Intravenous	9
Propofol	Intravenous	9
Vancomycin	Intravenous	8
Carvedilol	Tablet	8
Phenytoin	Intravenous	7
Clarithromycin	Intravenous	7
Tranexamic acid	Intravenous	7
Rifaximin	Tablet	7
Montelukast	Tablet	6
Ketorolac	Intravenous	6
Artemether	Intramuscular	5
Midazolam	Intravenous	5
Paracetamol	Syrup	5
Ciprofloxacin	Intravenous	4
Nimodipine	Tablet	4
Heparin	Subcutaneous	4
Haloperidol	Tablet	4
Fexofenadine	Tablet	4
Salmeterol+fluticasone	Inhalation	4
Epinephrine	Intravenous	4
Digoxin	Tablet	3
Clopidogrel	Tablet	3
Bisoprolol	Tablet	3
Furosemide+spironolactone	Tablet	3
Losartan	Tablet	3
Terlipressin	Intravenous	3
Valproate sodium	Intravenous	3
Atenolol	Tablet	3
Spironolactone	Tablet	3

Calcitriol	Intravenous	3
Atracurium	Intravenous	3
Mebendazole	Tablet	3
Valsartan+hydrochlorothiazide	Tablet	2
Valsartan	Tablet	2
Diltiazem	Tablet	2
Benzylpenicillin	Intravenous	2
Nitroglycerin	Tablet	2
Ceftazidime	Intravenous	2
Nifedipine	Tablet	2
Propranolol	Tablet	2
Levetiracetam	Tablet	2
Quinine	Intravenous	2
Artemether+lumefantrine	Tablet	2
Nalbuphine	Intravenous	2
Domperidone	Tablet	2
Lisinopril	Tablet	2
Diclofenac Na	Intravenous	2
Clonazepam	Tablet	2
Perindopril	Tablet	2
Oseltamivir	Intravenous	2
Montelukast	Granules	1
Nebivolol	Tablet	1
Escitalopram	Tablet	1
Metoprolol	Tablet	1
Cefixime	Tablet	1
Cefotaxime	Intravenous	1
Cefepime	Intravenous	1
Linezolid	Intravenous	1
Atropine	Intravenous	1
Carbamazepine	Tablet	1
Amlodipine+valsartan	Tablet	1
Colistimethate	Intravenous	1

Cefuroxime	Intravenous	1
Irbesartan	Tablet	1
Atorvastatin	Tablet	1
Streptomycin	Intramuscular	1
Ferrous sulfate+folic acid	Tablet	1
Levofloxacin	Intravenous	1
Esomeprazole	Tablet	1
Candesartan	Tablet	1
Rifmapin+isoniazid+pyrazinamide+ethambutol	Tablet	1
Sucralfate	Syrup	1
Carbimazole	Tablet	1
Pantoprazole	Tablet	1
Domperidone	Syrup	1
Metolazone	Tablet	1
Alprazolam	Tablet	1
Potassium chloride	Tablet	1
Furosemide	Tablet	1
Famotidine	Tablet	1
Dobutamine	Intravenous	1
Methylprednisolone	Intravenous	1
Erdosteine	Tablet	1
Thyroxine	Tablet	1
Azithromycin	Tablet	1
Paracetamol	Tablet	1
Verapamil	Tablet	1
Paracetamol	Intravenous	1
Pyridoxine	Tablet	1
Ondansetron	Intravenous	1
Isoniazid	Tablet	1
Epoetin alfa	Subcutaneous	1
Pyrazinamide	Tablet	1
Rifampin	Tablet	1

3.2.4.8 Indications

Secondary infection was the most prevalent indication in the MICU of NWGH & RC (228 cases of 1172) followed by asthma (156 cases), stress ulcer (151 cases), hypertension (46 cases) and respiratory tract infections (42 cases), while the rest of the cases were contributed by other indications.

3.2.4.9 Drug class

A total of 42 drug classes were used in the MICU of NWGH & RC with antibacterial being the most prevalent drug class as shown in Table 3.78.

Table 3.78 Frequencies of Drug classes used in MICU of NWGH& RC

Drug Class	Frequency
Antibacterial	330
Bronchodilator	126
Corticosteroids	120
Proton pump inhibitors	112
Anticoagulant	54
H2 receptor antagonists	48
Nutriceutical	30
Antiemetic	28
Vasopressor	28
Analgesic	26
Antiplatelet	24
Diuretic	24
Calcium channel blocker	23
Liver protectant	21
Beta blocker	20
HMG Co-A reductase inhibitor	17
Anticonvulsant	15
Sedative	14
Clotting activator	13
Antiviral	12
Antimalarial	9
ARBs	8
Hemostatic	8
Antianemic	8
Laxative	8
Leukotriene receptor antagonist	7
ACE inhibitor	5
H1 receptor antagonist	4
Antitubercular	4

Antipsychotic	4
Vasopressin	3
Musculoskeletal agent	3
Anthelmentic	3
Anxiolytic	2
Antiarrhythmic	2
Antithyroid agent	2
Nitrates	2
Cardiac glycoside	1
Cholinergic antagonist	1
Mucosal protective agents	1
Expectorant	1
Hematopoietic	1

3.2.4.10 Dosing errors in MICU of NWGH& RC

Out of the total 1172 cases, 134 (11.4%) had subtherapeutic doses while 69 (5.9%) had overdoses as shown in Table 3.79 and Table 3.80 respectively.

Table 3.79 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Piperacillin + Tazobactam	Intravenous	33
Ranitidine	Intravenous	24
Meropenem	Intravenous	14
Ceftriaxone	Intravenous	11
Imipenem + Cilastatin	Intravenous	5
Nimodipine	Tablets	4
Albuterol	Nebules	4
Ipratropium	Nebules	4
Hydrocortisone	Intravenous	3
Co-amoxiclav	Intravenous	3
Carvedilol	Tablets	3
Enoxaparin	Subcutaneous	3
Nitroglycerin	Tablets	2
Clarithromycin	Intravenous	2
Terlipressin	Intravenous	2
Phenytoin	Intravenous	2
Valsartan	Tablets	2
Metoprolol	Tablets	1
Diltiazem	Tablets	1
Rifaximin	Tablets	1
Perindopril	Tablets	1
Levetiracetam	Tablets	1
Propranolol	Tablets	1
Clonazepam	Tablets	1
Verapamil	Tablets	1
Ceftazidime	Intravenous	1
Dexamethasone	Intravenous	1
Metronidazole	Intravenous	1
Diclofenac sodium	intravenous	1
Montelukast	Granules	1

Table 3.80 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Albuterol	Nebules	19
Beclomethasone	Nebules	14
Ipratropium	Nebules	8
Dexamethasone	Intravenous	5
Enoxaparin	Subcutaneous	5
Furosemide	Intravenous	2
Esomeprazole	Intravenous	2
Tranexamic acid	Intravenous	2
Meropenem	Intravenous	2
Aspirin	Tablets	1
Phenytoin	Intravenous	1
Dimenhydrinate	Intravenous	1
Ranitidine	Intravenous	1
Cefepime	Intravenous	1
Calcitriol	Intravenous	1
Sucralfate	Syrup	1
Carbamazepine	Tablets	1
Amlodipine	Tablets	1
Clopidogrel+Enoxaparin	Tablets	1

3.2.5 Comparison of PDDIs among the hospitals

One-way ANOVA showed a significant difference (p=0.000) in the means of PDDIs among the four hospitals. Post HOC test (LSD) revealed that there was a significant difference (p=0.042) of PDDIs between NWGH & RC and HMC. A significant difference (p=0.000) was also present between KTH and LRH & HMC.

3.2.6 DISCUSSION

Patients admitted to the Medical Intensive Care Unit (MICU) have complex physiological and pathological conditions along with co-morbidities, complicating their condition. Multiple drug regimens are employed to treat these patients which increases the risk of potential drug-drug interactions (PDDIs). Thus studying the pattern of these PDDIs becomes imperative.

The prevalence of PDDIs in the MICU of the hospitals was observed to be 39.2%. The prevalence of PDDIs was similar to a Dutch university hospital evaluated 9644 ICU patient prescriptions of which 3892 had at least a single PDDI (40%),[234] while another Dutch study reported 34.7% PDDIs in the MICU.[73] A medical ICU was evaluated for PDDIs in India, reported 90.02% patients had at least one PDDI,[68] Brazilian studies conducted in ICUs reported 70%, 70.6% and 53.7% patients having a PDDI.[235,236,181] Although the present findings were similar to some studies, but differences in study design, ethnicity and population, and sensitivity of various drug-drug interactions checking databases contributed to the variations in results with some studies.

In the 3 government hospitals, LRH, KTH and HMC, 53, 96 and 50 interacting drug pairs were identified which contributed to 139, 254 and 125 potential drug-drug interactions, while in the NWGH & RC 84 interacting drug pairs were identified contributing to 183 PDDIs. Statistical analysis using One-way ANOVA revealed a significant difference ($p=0.042$) in PDDIs between NWGH & RC and HMC. Aspirin was used more frequently in the MICU of NWGH & RC as compared to HMC, which contributed to the significant difference in PDDIs between these two hospitals. One-way ANOVA also revealed a significant difference ($p=0.000$) in PDDIs between KTH

and LRH & HMC. In this instance carbamazepine was the drug which caused the significant prevalence of PDDIs in KTH as compared to LRH and HMC.

A high frequency of moderate and major severity PDDIs were observed in this study. The documentation of PDDIs was good or fair. Other studies also justifies these trends. An Indian study reported PDDIs of moderate severity and of good documentation to be the most prevalent.[68] Another study conducted in the MICU of a single hospital in Pakistan also reported moderate severity of PDDIs to be the most prevalent (49.6%) while the documentation of PDDIs was fair in 45.5% of the cases.[237] Moderate severity PDDIs were also noted to be most prevalent (61.2%) in an Ethiopian study.[177] Of the total PDDIs 71.7% were of moderate severity and 60% were of fair documentation in an Iranian study.[238] A Brazilian study also reported that 86% of the PDDIs were of major and moderate severity.[181] A Swiss study conducted in the medical wards reported 70.1% PDDIs to be of moderate severity while 69.4% were of good documentation.[239]

Most of the PDDIs encountered in the government hospital were of pharmacokinetic in nature and metabolism was the prominent mechanism for these PDDIs whereas in the private hospital the PDDIs were of pharmacodynamics type and synergism was the major mechanisms for PDDIs. This difference noted in both setups was due to the fact that aspirin was used in the private hospital very frequently and it resulted in multiple PDDIs of pharmacodynamic nature and synergistic mechanism.

This suggests that the nature of PDDIs depend on factors like the drugs used in a community, prescribing behavior of the prescriber and treatment patterns which varies from country to country and even varies among the hospitals in a country.

A significant association was found between number of interactions and number of prescribed drugs in this study. Various other studies have also reported a similar

association. An Ethiopian study revealed a significant association between these two factors when patient received three or more drugs.[177] Another Indian study reported a significant positive association between these two factors.[178] While various Pakistani, Iranian, Brazilian, Italian, Swedish and American studies also reported a significant association between number of interactions and number of prescribed drugs.[81,84,63,59,179] No significant association was found between duration of stay and number of interactions. A similar non-significant association was reported in another study conducted in an ICU of a university hospital.[180]

Potential drug-drug interactions were most prevalent among antibiotics, antivirals, antiplatelet, anticoagulant, anticonvulsants and corticosteroids. The involvement of these classes in PDDIs are reported by a number of studies. A Swiss study reported that anticoagulants and antiplatelets were involved in 13.5% of all the PDDIs in medical wards.[240] Similarly, studies conducted in the ICUs of hospitals in Netherland also reported anticonvulsants, cortisteroids, antivirals, and anticoagulants to be the frequently involved drug classes in PDDIs.[73,234] Brazilian studies also reported the involvement of antibiotics, anticoagulants, anticonvulsants and corticosteroids as the major classes responsible for PDDIs.[236,181] Corticosteroids and anticonvulsants were the main classes involved in PDDIs in an Indian study conducted in the MICU of a hospital.[68] The high risks involved with these drug combinations can be managed by following recommended guidelines.

3.2.7 Management guidelines for clinically significant PDDIs

Potential drug-drug interactions having a severity of major or moderate with excellent or good documentation were considered clinically significant and were rated values as 1 and 2. Using this criteria along with the frequency of PDDIs, a list of 12 interacting drug pairs was considered important clinically, because of the associated high risk and occurrence in the medical intensive unit.

3.2.7.1 Clarithromycin + Carbamazepine

The exposure of carbamazepine may be increased, while the exposure of clarithromycin may be decreased when these two drugs are used concomitantly. This is due to the CYP3A4 enzyme inhibition by clarithromycin which inhibits the metabolism of carbamazepine, while the metabolism of clarithromycin is increased by the CYP3A4 enzyme induction ability of carbamazepine. It is recommended to avoid simultaneous administration of these two drugs, however, if it is unavoidable, close monitoring and adjustments of dose of both the drugs is recommended.[119]

3.2.7.2 Aspirin + Enoxaparin

The concomitant use of aspirin and enoxaparin results of an increased risk of bleeding. In patients receiving spinal anesthesia or undergoing a spinal puncture, the drug combination may cause epidural or spinal hematomas. However, it is used in myocardial infarction and ischemic conditions of the heart where this PDDI may be considered as beneficial, because of its synergistic action on decreasing platelet function and coagulation. Patients should be monitored closely for any sign and symptom of bleeding and treated accordingly otherwise.[102,100]

3.2.7.3 Clopidogrel + Omeprazole

Simultaneous use of clopidogrel with omeprazole or esomeprazole may reduce clopidogrel clinical efficacy and increase the risk of thrombosis. Clopidogrel is converted into its active metabolite by the action of CYP2C19 enzyme, while omeprazole and esomeprazole has an inhibitory effect on this enzyme resulting in the interaction. Omeprazole and esomeprazole is recommended to be replaced with other drugs like pantoprazole or lansoprazole when administering concomitantly with clopidogrel.[137,241,242,138]

3.2.7.4 Hydrocortisone + Moxifloxacin

Concurrent use of hydrocortisone and moxifloxacin may increase the risk of tendon rupture. Moxifloxacin and other fluoroquinolones cause tendonitis and this risk is increased when simultaneously used with hydrocortisone and other corticosteroids. The mechanism for this interaction is unknown and further research can be performed to elucidate its mechanism.[243]

3.2.7.5 Aspirin + Dexamethasone

The concurrent use of aspirin with dexamethasone may increase the risk of gastrointestinal bleeding and reduced plasma concentrations of aspirin. The synergistic action of both these drugs is the responsible mechanism for this adverse reaction. Moreover, dexamethasone increases the clearance of aspirin. Monitoring signs and symptoms of gastrointestinal bleeding along with the effectiveness of aspirin is recommended.[114]

3.2.7.6 Dexamethasone + Rifampin

The effectiveness of dexamethasone is decreased when used concomitantly with rifampin. Rifampin induces the metabolism of dexamethasone decreasing its plasma concentration. Patient should be monitored for the effectiveness of dexamethasone and its dose may be increased.[120]

3.2.7.7 Acyclovir + Valproate Sodium/Phenytoin

Valproate and phenytoin plasma concentrations may be decreased when used concurrently with acyclovir. Although the mechanism is not fully understood but changes in gastrointestinal transit and pH may be responsible. Management includes monitoring of plasma levels of the anticonvulsant or replacing the antiviral.[195]

3.2.7.8 Rifampin + Valproate Sodium

Concurrent use of rifampin with valproate may decrease plasma concentrations of valproate. Rifampin increases the clearance of valproate which is responsible for its decreased plasma concentrations. Monitoring of valproate plasma levels and dose adjustment is recommend when used simultaneously with rifampin.[28]

3.2.7.9 Carbamazepine + Metronidazole

Carbamazepine serum concentrations may increase resulting in its toxicity when used concurrently with metronidazole. The mechanism is not known completely but it is suggested that metronidazole may inhibit the metabolism of carbamazepine. Monitoring of carbamazepine plasma concentrations and signs and symptoms of its toxicity like nausea, dizziness, diplopia and CNS effects, along with its dose adjustment is recommended.[196]

3.2.7.10 Nimodipine + Valproate Sodium

Simultaneous administration of nimodipine and valproate may lead to nimodipine toxicity displayed by dizziness, headache, flushing and peripheral edema. Decreased metabolism of nimodipine is responsible for this interaction and downward adjustment of the dose of nimodipine is required in this case.[107]

3.2.7.11 Dexamethasone + Phenytoin

Dexamethasone effectiveness may be decreased when used in combination with phenytoin due to the increased metabolism of dexamethasone in the presence of phenytoin. Monitoring of the therapeutic effect of dexamethasone is recommended and a 2 times or more increase in the dose of dexamethasone may be required. Phenytoin plasma concentrations should also be monitored as it can also be altered.[186]

3.3 CARDIAC INTENSIVE CARE UNIT (CCU)

3.3.1 Lady Reading Hospital (LRH)

3.3.1.1 General Patient Characteristics

In CCU of LRH, a total of 260 patients were studied, out of which 172 (66.2%) were males and 88 (33.8%) were females. The mean age of the population was 55.24 and ranged from 12 to 95 years. Of the total patients, 55.4% patients were between the ages of 19 to 59 years, 0.8% were of 18 years and below, while 43.8% patients were of 60 years and above. Mean duration of stay in the critical care unit and mean number of prescribed drugs were 3.73 ± (2.27) days and 5.70 ± (1.33) drugs respectively as shown in Table 3.81.

The top three leading causes of admission in the CCU of LRH were myocardial infarction, acute coronary syndrome and heart failure as shown in Figure 3.9.

Table 3.81 General Patient Characteristics in the CCU of LRH

Variables	**Frequency (%)**
Gender	
Male	172 (66.2%)
Female	88 (33.8%)
Age (years)	
Mean ± SD	55.24 (± 13.58)
Median	55
Range	12-95
≤ 18	2 (0.8%)
19-59	144 (55.4%)
≥ 60	114 (43.8%)
Drugs prescribed per patient	
Mean ± SD	5.70 ± (1.33)
Median	6
Range	2-10
≤ 4	44 (16.9%)
5-6	158 (60.8%)
≥ 7	58 (22.3%)
Stay in ICU (days)	
Mean ± SD	3.73 ± (2.27)
Median	3
Range	2-30
≤ 2	54 (20.7%)
3-5	151 (58.1%)
≥ 6	55 (21.2%)

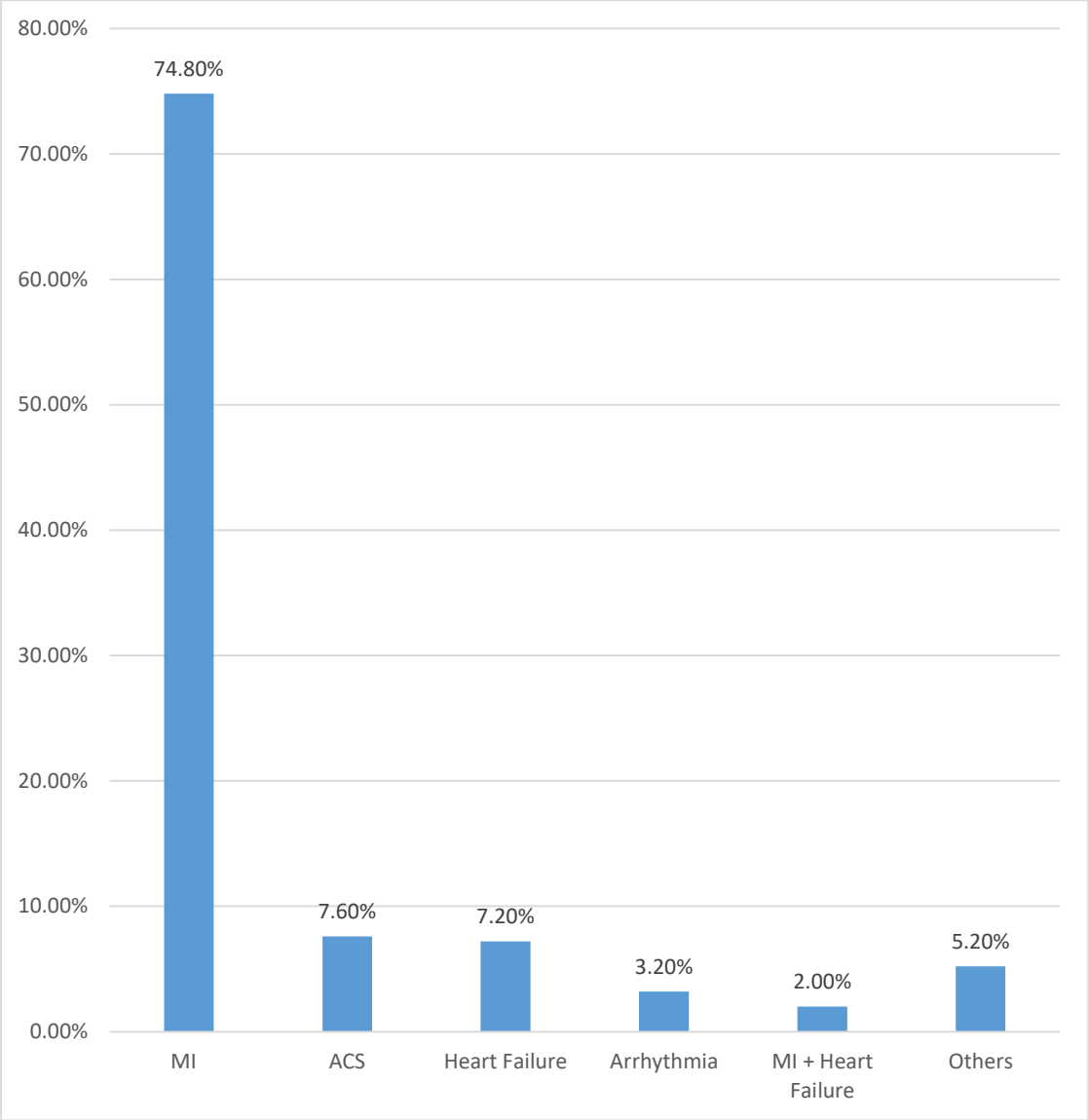

Figure 3.9 Causes of admission to CCU of LRH

3.3.1.2 Prevalence of Potential drug-drug interactions

A prevalence of 96.9% PDDIs was reported in the patients of CCU of LRH. Of the total 260 patients, seventy eight patients encountered 5 PDDIs while one patient encountered 12 PDDIs as shown in Table 3.82.

Table 3.82 Prevalence of PDDIs in the CCU of LRH

No. of PDDIs	Frequency	Percentage %
1	12	4.6
2	13	5.0
3	28	10.8
4	48	18.5
5	78	30
6	40	15.4
7	16	6.2
8	10	3.8
9	4	1.5
10	2	0.8
12	1	0.4

3.3.1.3 Categories of PDDIs

The PDDIs reported in the CCU of LRH were classified on the basis of severity, documentation, onset and clinical significance. The type and mechanisms of interactions were also identified. A total of 76 interacting drug pairs were identified which caused 1204 drug-drug interactions. The severity of 53.1% PDDIs were major, 46.8% PDDIs moderate and 0.1% PDDIs were minor. The documentation of 43% PDDIs was fair, 51% PDDIs were of good and 6% of the PDDIs were of excellent documentation. According to the onset of PDDIs, 16.1% were of rapid onset, 21.2% were of delayed onset while 62.7% were of unknown onset. In terms of type of PDDIs, pharmacokinetics contributed to 20.9% PDDIs and pharmacodynamics contributed to

78.6% PDDIs, while 0.5% PDDIs were of unknown type. In terms of mechanism, synergism contributed as the mechanism in 53.6% PDDIs, antagonism was involved in 25% PDDIs, absorption contributed to 0.3% PDDIs, metabolism contributed for 4% PDDIs, elimination contributed in 16.6% PDDIs, while 0.5% PDDIs were of unknown mechanism as shown in Table 3.83.

Table 3.83 Categories of PDDIs in the CCU of LRH

Variable	**Frequency (%)**
Severity of PDDIs	
Major	639 (53.1%)
Moderate	563 (46.8%)
Minor	2 (0.1%)
Documentation of PDDIs	
Excellent	72 (6.0%)
Good	614 (51.0%)
Fair	518 (43.0%)
Onset of PDDIs	
Rapid	194 (16.1%)
Delayed	255 (21.2%)
Unkonwn	755 (62.7%)
Type of Interaction	
Pharmacodynamic	946 (78.6%)
Pharmacokinetic	252 (20.9%)
Unknown	6 (0.5%)
Mechanism of Interaction	
Synergism	645 (53.6%)
Antagonism	301 (25.0%)
Absorption	4 (0.3%)
Metabolism	48 (4.0%)
Elimination	200 (16.6%)
Unknown	6 (0.5%)

3.3.1.4 Interacting Drug Pairs

In the CCU of LRH, 76 interacting drug pairs were identified causing 1204 drug-drug interactions, of these interacting drug pairs, 7 were involved in 825 (68.5%) interactions of which 3 were major and 4 were moderate as shown in Table 3.84.

Table 3.84 Interacting drug pairs in the CCU of LRH

Interacting Pair	Frequency	Percentage
aspirin-clopidogrel	206	17.1%
aspirin-enoxaparin	161	13.4%
clopidogrel-enoxaparin	160	13.3%
aspirin-bisoprolol	87	7.2%
aspirin-ramipril	84	7.0%
aspirin-nitroglycerin	68	5.6%
aspirin-furosemide	59	4.9%
aspirin-metoprolol	42	3.5%
aspirin-spironolactone	35	2.9%
aspirin-lisinopril	27	2.2%
clopidogrel-fondaparinux	22	1.8%
aspirin-fondaparinux	22	1.8%
digoxin-furosemide	20	1.7%
ramipril-furosemide	18	1.5%
atorvastatin-clopidogrel	18	1.5%
aspirin-candesartan	17	1.4%
digoxin-spironolactone	15	1.2%
ramipril-spironolactone	11	0.9%
clopidogrel-omeprazole	9	0.7%
aspirin-valsartan	9	0.7%
enoxaparin-warfarin	8	0.7%
aspirin-carvedilol	7	0.6%

aspirin-warfarin	5	0.4%
amlodipine-bisoprolol	5	0.4%
aspirin-losartan	5	0.4%
candesartan-spironolactone	4	0.3%
aspirin-glimepiride	4	0.3%
bisoprolol-glimepiride	4	0.3%
furosemide-lisinopril	3	0.2%
amlodipine-aspirin	3	0.2%
aspirin-hydrochlorothiazide	3	0.2%
rosuvastatin-warfarin	3	0.2%
clopidogrel-warfarin	3	0.2%
aspirin-ranitidine	2	0.2%
aspirin-amlodipine	2	0.2%
amlodipine-clopidogrel	2	0.2%
bisoprolol-digoxin	2	0.2%
spironolactone-valsartan	2	0.2%
spironolactone-warfarin	2	0.2%
bisoprolol-metformin	2	0.2%
digoxin-metoprolol	2	0.2%
clopidogrel-rabeprazole	2	0.2%
amiodarone-clopidogrel	2	0.2%
aspirin-enalapril	2	0.2%
amiodarone-rosuvastatin	2	0.2%
lisinopril-spironolactone	2	0.2%
aspirin-telmisartan	2	0.2%
losartan-spironolactone	1	0.1%
captopril-spironolactone	1	0.1%
dexamethasone-rifampin	1	0.1%
captopril-furosemide	1	0.1%
clarithromycin-digoxin	1	0.1%
amiodarone-bisoprolol	1	0.1%

digoxin-esomeprazole	1	0.1%
aspirin-captopril	1	0.1%
clopidogrel-esomeprazole	1	0.1%
amiodarone-ranitidine	1	0.1%
aspirin-dexamethasone	1	0.1%
atorvastatin-digoxin	1	0.1%
ceftriaxone-warfarin	1	0.1%
paracetamol-warfarin	1	0.1%
aspirin-nebivolol	1	0.1%
aspirin-diltiazem	1	0.1%
clopidogrel-diltiazem	1	0.1%
enalapril-furosemide	1	0.1%
furosemide-gentamicin	1	0.1%
cephradine-warfarin	1	0.1%
bisoprolol-methyldopa	1	0.1%
metformin-metoprolol	1	0.1%
amiodarone-metoprolol	1	0.1%
ceftazidime-warfarin	1	0.1%
telmisartan-aspirin	1	0.1%
digoxin-telmisartan	1	0.1%
ceftizoxime-warfarin	1	0.1%
cefoperazone-warfarin	1	0.1%
spironolactone-telmisartan	1	0.1%

3.3.1.5 Clinically significant PDDIs in the CCU of LRH

Analysis of the drug interaction pairs for clinical significance yielded 55 pairs having a clinical significance 1 or 2. These pairs contributed to 54.9% of the total PDDIs (661 of 1204) of which 15 were of clinically significance 1 while 40 were of clinical significance 2. The clinically significant drug interaction pairs along with their potential outcomes are shown in Table 3.85.

Table 3.85 Clinically important interacting pairs and their potential outcomes in CCU of LRH

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Aspirin-enoxaparin	1	161	Increased risk of bleeding.	105,106
Ramipril-spironolactone	1	11	May result in hyperkalemia.	189-190,
Lisinopril-spironolactone	1	2	May result in hyperkalemia.	190
Captopril-spironolactone	1	1	May result in hyperkalemia.	189,190
Clopidogrel-omeprazole	1	10	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	138,139
Amlodipine-clopidogrel	1	2	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Clarithromycin-digoxin	1	1	May result in digoxin toxicity (nausea, vomiting, arrhythmias).	223,224
Amiodarone-bisoprolol	1	1	Hypotension, bradycardia, or cardiac arrest.	244
Ceftazidime-warfarin	1	2	Increased risk of bleeding.	134
Cephradine-warfarin	1	1	Increased risk of bleeding.	134
Clopidogrel-rabeprazole	1	2	May result in increased risk for thrombosis.	139,241
Digoxin-spironolactone	1	15	May result in increased digoxin exposure.	245

Furosemide-gentamicin	1	1	Increased gentamicin plasma and tissue concentrations and additive ototoxicity and/or nephrotoxicity.	[246]
Aspirin-warfarin	1	5	Increased risk of bleeding.	[22,23]
Clopidogrel-diltiazem	1	1	Decreased antiplatelet effect and increased risk of thrombotic events.	[207,208]
Dexamethasone-rifampin	2	1	May result in decreased dexamethasone effectiveness	[120]
Aspirin-dexamethasone	2	1	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[142,115]
Aspirin-metoprolol	2	32	May result in decreased antihypertensive effect.	[165]
Aspirin-nitroglycerin	2	68	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	[124,125]
Furosemide-lisinopril	2	3	May result in postural hypotension (first dose).	[151]
Furosemide-ramipril	2	18	May result in postural hypotension (first dose).	[151]
Furosemide-captopril	2	1	May result in postural hypotension (first doe).	[151]
Furosemide-enalapril	2	1	May result in postural hypotension (first dose).	[151]
Aspirin-furosemide	2	51	May result in decreased diuretic and antihypertensive efficacy.	[121,122]
Aspirin-spironolactone	2	35	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.	[123]

Aspirin-carvedilol	2	7	May result in decreased antihypertensive effect.	[124,125]
Aspirin-nebivolol	2	1	May result in decreased antihypertensive effect.	[124,125]
Aspirin-bisoprolol	2	87	May result in decreased antihypertensive effect.	[124,125]
Aspirin-losartan	2	5	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-valsartan	2	6	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-candesartan	2	16	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Telmisartan-aspirin	2	3	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-amlodipine	2	5	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[141]
Aspirin-hydrochlorothiazide	2	3	Decreased diuretic and antihypertensive efficacy.	[145]
Amlodipine-bisoprolol	2	5	May result in hypotension and/or bradycardia.	[152,153]
Digoxin-furosemide	2	20	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[213]
Aspirin-diltiazem	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Aspirin-lisinopril	2	27	May result in decreased lisinopril effectiveness.	[230]

Aspirin-captopril	2	1	May result in decreased captopril effectiveness.	230
Aspirin-enalapril	2	2	May result in decreased enalapril effectiveness.	230
Amiodarone-clopidogrel	2	2	Ineffective inhibition of platelet aggregation.	176
Amiodarone-rosuvastatin	2	2	Elevations in serum transaminase levels.	247
Rosuvastatin-warfarin	2	3	Increase in international normalized ratio (INR) and increased risk of bleeding.	248
Aspirin-glimepiride	2	4	Increased risk of hypoglycemia.	249
Atorvastatin-digoxin	2	1	Increased plasma concentrations of digoxin.	250
Bisoprolol-digoxin	2	2	Increased risk of bradycardia and possible digitalis glycoside toxicity.	251
Bisoprolol-glimepiride	2	4	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	252
Bisoprolol-methyldopa	2	1	Exaggerated hypertensive response, tachycardia, or arrhythmias during physiologic stress or exposure to exogenous catecholamines.	253
Bisoprolol-metformin	2	2	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	252
Digoxin-metoprolol	2	2	Increased risk of bradycardia and possible digitalis glycoside toxicity.	232
Digoxin-telmisartan	2	1	Increased risk of digoxin toxicity (nausea, vomiting, arrhythmias).	254

Metformin-metoprolol	2	1	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Atorvastatin-clopidogrel	2	18	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.	[210]
Paracetamol-warfarin	2	1	Increased risk of bleeding.	[255]
Ceftriaxone-warfarin	2	1	Increased risk of bleeding.	[158]

3.3.1.6 Association of PDDIs with other parameters in the CCU of LRH

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 5 or more drugs (OR =8.552; 95%CI = 1.927-37.956; p = 0.005). An insignificant association was found between the presence of PDDIs with duration of stay of 4 or more days (OR = 0.393; 95%CI = 0.85-1.812; p = 0.231), and with gender (OR = 3.124; 95%CI = 0.365-26.751; p = 0.299). The results are shown in Table 3.86.

Table 3.86 logistic regression analysis in the CCU of LRH

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=252)	**Interactions absent (n=8)**		
Prescribed drugs				
< 5	39	5		
≥ 5	213	3	8.552 (1.927-37.956)	0.005
Duration of stay				
< 4	200	5		
≥ 4	52	3	0.393(0.85-1.812)	0.231
Gender				
Male	165	7		
Female	87	1	3.124 (0.365-26.751)	0.299

3.3.1.7 Drugs used

A total of 78 drugs were prescribed in the CCU of LRH appearing 1480 times in all the medication charts as shown in Table 3.87.

Table 3.87 Frequencies of commonly used drugs in the CCU of LRH

Drug Name	Dosage Form	Frequency
Aspirin	Tablets	206
Clopidogrel	Tablets	184
Rosuvastatin	Tablets	181
Enoxaparin	Subcutaneous	171
Bisoprolol	Tablets	91
Ramipril	Tablets	91
Nitroglycerin	Tablets	74
Furosemide	Intravenous	55
Metoprolol	Tablets	43
Spironolactone	Tablets	30
Clopidogrel+aspirin	Tablets	28
Lisinopril	Tablets	27
Fondaparinux	Subcutaneous	22
Digoxin	Tablets	21
Atorvastatin	Tablets	21
Candesartan	Tablets	19
Co-amoxiclav	Intravenous	17
Furosemide+spironolactone	Tablets	14
Beclomethasone	Nebules	13
Ipratropium	Nebules	12
Ceftizoxime	Intravenous	11
Trimetazidine	Tablets	11
Isosorbide mononitrate	Tablets	10
Omeprazole	Intravenous	9
Warfarin	Tablets	9

Valsartan	Tablets	7
Carvedilol	Tablets	7
Ceftriaxone	Intravenous	6
Furosemide	Tablets	6
Losartan	Tablets	5
Amlodipine	Tablets	5
Nicorandil	Tablets	5
Amiodarone	Tablets	4
Glimepiride	Tablets	4
Dexamethasone	Intravenous	3
Gliclazide	Tablets	3
Pantoprazole	Tablets	3
Ranitidine	Intravenous	2
Moxifloxacin	Intravenous	2
Ranitidine	Tablets	2
Metronidazole	Intravenous	2
Ceftazidime	Intravenous	2
Enalapril	Tablets	2
Sucralfate	Syrup	2
Telmisartan+hydrochlorothiazide	Tablets	2
Metformin	Tablets	2
Rabeprazole	Tablets	2
Telmisartan	Tablets	2
Cefoperazone+sulbactam	Intravenous	1
Ciprofloxacin	Intravenous	1
Esomeprazole	Intravenous	1
Nebivolol	Tablets	1
Albuterol	Nebules	1
Valsartan+hydrochlorothiazide	Tablets	1
Losartan+hydrochlorothiazide	Tablets	1
Diltiazem	Tablets	1
Cefixime	Tablets	1
Prednisolone	Tablets	1

Clarithromycin	Intravenous	1
Benzylpenicillin	Intravenous	1
Amlodipine+valsartan	Tablets	1
Cephradine	Intravenous	1
Sitagliptin+metformin	Tablets	1
Propranolol	Tablets	1
Omeprazole	Tablets	1
Paracetamol+orphenadrine	Tablets	1
Pitavastatin	Tablets	1
Esomeprazole	Tablets	1
Isosorbide dinitrate	Tablets	1
Captopril	Tablets	1
Methyldopa	Tablets	1
Rifmapin+isoniazid+pyrazinamide+ethambutol	Tablets	1
Domperidone	Syrup	1
Gentamicin	Intravenous	1
Dexamethasone	Tablets	1
Cephradine	Tablets	1
Pyridoxine	Tablets	1
Tramadol	Tablets	1

3.3.1.8 Indications

Myocardial infarction was the most prevalent indication in the CCU of LRH (619 cases of 1480) followed by hyperlipidemia (203 cases), hypertension (188 cases), angina (117 cases), heart failure (107 cases), thrombosis (73 cases), secondary infections (42 cases) and edema (35 cases), while the rest of the cases were contributed by other indications.

3.3.1.9 Drug class

A total of 26 drug classes were used in the CCU of LRH with antiplatelet being the most prevalent drug class as shown in Table 3.88.

Table 3.88 Frequencies of Drug classes used in the CCU of LRH

Drug Class	Frequency
Antiplatelet	417
HMG Co-A reductase inhibitor	203
Anticoagulant	202
Beta blocker	143
ACE inhibitor	121
Diuretic	104
Nitrates	85
Antibacterial	47
ARBs	38
Cardiac glycoside	21
Corticosteroid	18
PPI	18
Anti ischemic agent	16
Bronchodilator	13
Sulfonyl ureas	7
Calcium channel blocker	6
H2 receptor antagonist	4
Antiarrhythmic	4
Analgesic	2
Mucosal protective agents	2
Biguanides	2
Antiemetic	1
Sulfonyl urea+biguanides	1
Alpha adrenergic agonist	1
Nutriceutical	1
Antitubercular	1

3.3.1.10 Dosing errors in the CCU of LRH

Out of the total 1478 cases, 122 (8.3%) had subtherapeutic doses while 21 (1.4%) had overdoses as shown in Table 3.89 and Table 3.90 respectively.

Table 3.89 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Nitroglycerin	Tablets	68
Ramipril	Tablets	21
Candesartan	Tablets	5
Co-amoxiclav	Intravenous	5
Valsartan	Tablets	4
Carvedilol	Tablets	3
Trimetazidine	Tablets	3
Cefotaxime	Intravenous	2
Ceftizoxime	Intravenous	2
Ceftazidime	Intravenous	1
Propranolol	Tablets	1
Methyldopa	Tablets	1
Amiodarone	Tablets	1
Metoprolol	Tablets	1
Lisinopril	Tablets	1
Diltiazem	Tablets	1
Metformin	Tablets	1
Nicorandil	Tablets	1

Table 3.90 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Beclomethasone	Nebules	7
Dexamethasone	Intravenous	2
Cephradine	Intravenous	2
Sucralfate	Syrup	2
Metoprolol	Tablets	2
Spironolactone	Tablets	2
Isosorbide mononitrate	Tablets	2
Dexamethasone	Tablets	1
Moxifloxacin	Intravenous	1

3.3.2 Khyber Teaching Hospital (KTH)

3.3.2.1 General Patient Characteristics

In CCU of KTH 260 patients were analyzed, of which 154 (59.2%) were males and 106 (40.8%) were females. The mean age of the population was 56.67 years and ranged from 17 to 100 years. Of the total patients, 52.4% were between the ages of 19 to 59 years, 46.9% were of 60 years and older and 0.4% were of 18 years and below. Mean duration of stay in the critical care unit was 3.73 ± (1.44) days, while the mean number of prescribed drugs were 5.79 ± (1.67) as shown in Table 3.91.

The top three leading causes of admission in the CCU of KTH were myocardial infarction, acute coronary syndrome and heart failure as shown in Figure 3.10

Table 3.91 General Characteristics of Patients in CCU of KTH

Variables	**Frequency (%)**
Gender	
Male	154 (59.2%)
Female	106 (40.8%)
Age (years)	
Mean ± SD	56.67 (± 13.44)
Median	55
Range	17-100
≤ 18	1 (0.4%)
19-59	137 (52.7%)
≥ 60	122 (46.9%)
Drugs prescribed per patient	
Mean ± SD	5.79 ± (1.67)
Median	6
Range	2-12
≤ 4	60 (23.1%)
5-6	117 (45.0%)
≥ 7	83 (31.9%)
Stay in ICU (days)	
Mean ± SD	3.73 ± (1.44)
Median	3
Range	2-13
≤ 2	35 (13.4%)
3-5	171 (65.8%)
≥ 6	54 (20.8%)

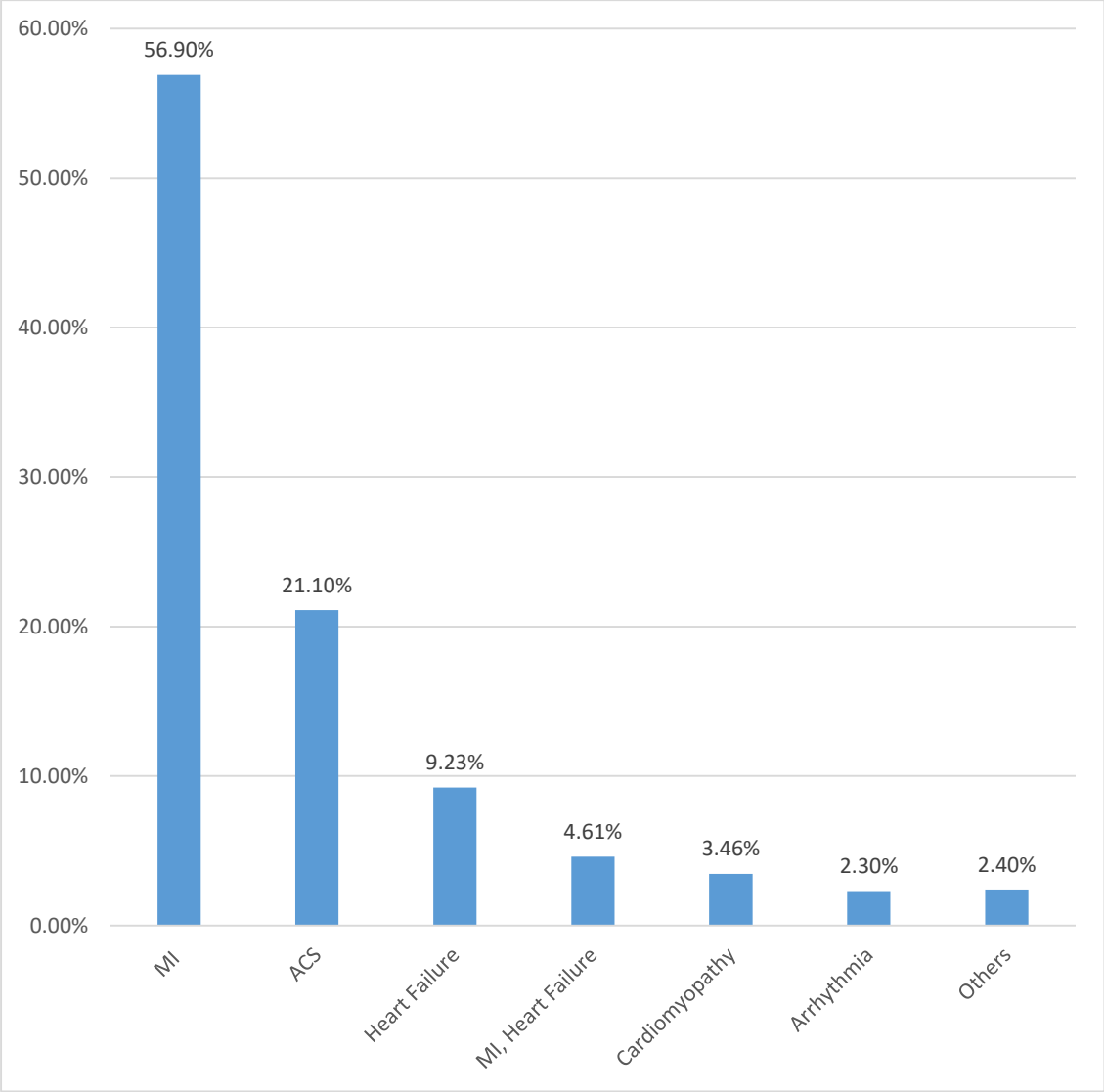

Figure 3.10 Causes of admission to CCU of KTH

3.3.2.2 Prevalence of Potential drug-drug interactions

The prevalence of PDDIs in patients of CCU of KTH was reported to be 96.5%. Of the total 260 patients, 21.5% patients had 5 PDDIs while 1.2% patients had 12 PDDIs, details of the prevalence of PDDIs is shown in Table 3.92.

Table 3.92 Prevalence of PDDIs in CCU of KTH

No. of PDDIs	Frequency	Percentage %
1	16	6.2
2	13	5.0
3	27	10.4
4	38	14.6
5	56	21.5
6	43	16.5
7	27	10.4
8	11	4.2
9	4	1.5
10	9	3.5
11	4	1.5
12	3	1.2

3.3.2.3 Categories of PDDIs

Severity, documentation, onset, type and mechanism of interactions were the parameters used to classify the PDDIs reported in the CCU of KTH. A total of 95 interacting drug pairs were identified which caused 1295 drug-drug interactions. According to severity 45.2% of the PDDIs were major, 52.6% were moderate and 4.3% were minor while 2.2% were contraindicated. Based on documentation of PDDIs, 16.5% were of excellent documentation, 47.1% were of good and 36.4% were of fair documentation. The onset of 18% PDDIs was rapid while 22.9% were of delayed and 59.1% were of unknown onset. According to type of interactions, 32.1% PDDIs were

of pharmacokinetic nature and 66.9% PDDIs were of pharmacodynamic nature while 1% PDDIs were of unknown type. In terms of mechanism, synergism contributed in 44.5% PDDIs, antagonism was involved in 22.5% PDDIs, absorption contributed to 2.5% PDDIs, metabolism contributed for 13.9% PDDIs, elimination contributed in 15.2% PDDIs, combination of absorption and metabolism contributed in 0.4% PDDIs while 1% PDDIs were of unknown mechanisms as shown in Table 3.93.

Table 3.93 Categories of PDDIs in CCU of KTH

Variable	**Frequency (%)**
Severity of PDDIs	
Major	585 (45.2%)
Moderate	681 (52.6%)
Minor	29 (2.2%)
Documentation of PDDIs	
Excellent	214 (16.5%)
Good	610 (47.1%)
Fair	471 (36.4%)
Onset of PDDIs	
Rapid	233 (18%)
Delayed	297 (22.9%)
Unkonwn	765 (59.1%)
Type of Interaction	
Pharmacodynamic	867 (66.9%)
Pharmacokinetic	415 (32.1%)
Unknown	13 (1.0%)
Mechanism of Interaction	
Synergism	577 (44.5%)
Antagonism	291 (22.5%)
Absorption	32 (2.5%)
Metabolism	180 (13.9%)
Elimination	197 (15.2%)
Absorption/Metabolism	5 (0.4%)
Unknown	13 (1.0%)

3.3.2.4 Interacting Drug Pairs

In the CCU of KTH, 95 interacting drug pairs were identified causing 1295 drug-drug interactions, of these interacting drug pairs, 7 were involved in 813 (62.7%) interactions of which 3 were major and 4 were moderate as shown in Table 3.94.

Table 3.94 Interacting drug pairs in CCU of KTH

Interacting Pair	Frequency	Percentage
aspirin-clopidogrel	204	15.8%
aspirin-enoxaparin	131	10.1%
clopidogrel-enoxaparin	126	9.7%
atorvastatin-clopidogrel	97	7.5%
aspirin-nitroglycerin	87	6.7%
aspirin-ramipril	84	6.5%
aspirin-metoprolol	84	6.5%
aspirin-furosemide	57	4.4%
clopidogrel-esomeprazole	40	3.1%
ramipril-furosemide	33	2.5%
aspirin-ranitidine	26	2.0%
aspirin-carvedilol	24	1.9%
aspirin-losartan	23	1.8%
digoxin-furosemide	21	1.6%
aspirin-bisoprolol	18	1.4%
aspirin-captopril	16	1.2%
aspirin-spironolactone	14	1.1%
aspirin-lisinopril	13	1.0%
aspirin-hydrochlorothiazide	11	0.8%
ramipril-spironolactone	11	0.8%
clopidogrel-fondaparinux	9	0.7%
aspirin-fondaparinux	9	0.7%

losartan-spironolactone	8	0.6%
atorvastatin-diltiazem	8	0.6%
digoxin-spironolactone	8	0.6%
clopidogrel-diltiazem	8	0.6%
aspirin-glimepiride	7	0.5%
aspirin-diltiazem	7	0.5%
captopril-furosemide	6	0.5%
digoxin-omeprazole	5	0.4%
digoxin-metoprolol	4	0.3%
aspirin-dexamethasone	4	0.3%
atorvastatin-digoxin	4	0.3%
carvedilol-digoxin	4	0.3%
amlodipine-clopidogrel	3	0.2%
clopidogrel-omeprazole	3	0.2%
lisinopril-furosemide	3	0.2%
aspirin-levofloxacin	3	0.2%
ciprofloxacin-metoprolol	3	0.2%
glimepiride-metoprolol	3	0.2%
aspirin-warfarin	2	0.2%
enoxaparin-warfarin	2	0.2%
aspirin-amlodipine	2	0.2%
aspirin-candesartan	2	0.2%
spironolactone-warfarin	2	0.2%
bisoprolol-metformin	2	0.2%
digoxin-esomeprazole	2	0.2%
ciprofloxacin-metronidazole	2	0.2%
captopril-digoxin	2	0.2%
metoprolol-ranitidine	2	0.2%
metformin-metoprolol	2	0.2%
atorvastatin-clarithromycin	1	0.1%
co-amoxiclav-warfarin	1	0.1%

captopril-spironolactone	1	0.1%
amiloride-aspirin	1	0.1%
salmeterol-levofloxacin	1	0.1%
salmeterol-metoprolol	1	0.1%
carvedilol-verapamil	1	0.1%
aspirin-valsartan	1	0.1%
amlodipine-aspirin	1	0.1%
spironolactone-valsartan	1	0.1%
amlodipine-carvedilol	1	0.1%
amiodarone-ranitidine	1	0.1%
amiodarone-carvedilol	1	0.1%
aspirin-nifedipine	1	0.1%
propranolol-verapamil	1	0.1%
aspirin-heparin	1	0.1%
clopidogrel-verapamil	1	0.1%
clopidogrel-dalteparin	1	0.1%
amiloride-losartan	1	0.1%
levofloxacin-prednisolone	1	0.1%
aspirin-enalapril	1	0.1%
amiodarone-fexofenadine	1	0.1%
clopidogrel-heparin	1	0.1%
amlodipine-ciprofloxacin	1	0.1%
aspirin-irbesartan	1	0.1%
esomeprazole-propranolol	1	0.1%
digoxin-amiloride	1	0.1%
losartan-ramipril	1	0.1%
bisoprolol-glimepiride	1	0.1%
aspirin-verapamil	1	0.1%
hydrochlorothiazide-propranolol	1	0.1%
lisinopril-spironolactone	1	0.1%
amoxicillin-warfarin	1	0.1%

diltiazem-metoprolol	1	0.1%
carvedilol-glimepiride	1	0.1%
digoxin-hydrochlorothiazide	1	0.1%
carvedilol-doxazosin	1	0.1%
amlodipine-metoprolol	1	0.1%
aspirin-glyburide	1	0.1%
bisoprolol-glyburide	1	0.1%
glimepiride-levofloxacin	1	0.1%
digoxin-metformin	1	0.1%
ranitidine-metformin	1	0.1%
glyburide-hydrochlorothiazide	1	0.1%

3.3.2.5 Clinical importance of PDDIs in CCU of KTH

Clinically significant PDDIs were identified using the predetermined criterion and analysis resulted in the identification of 61 interacting pairs which were of clinical significance 1 and 2. These 61 pairs contributed to 62.1% of the total potential drug-drug interactions (804 of 1295), of which 21 were of clinically significance 1 while 40 were of clinical significance 2. These clinically significant PDDIs along with their potential outcomes are shown in Table 3.95.

Table 3.95 Clinically important interacting pairs and their potential outcomes in CCU of KTH

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Aspirin-enoxaparin	1	131	Increased risk of bleeding.	105,106
Clopidogrel-omeprazole	1	3	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	136,137
Ramipril-spironolactone	1	11	May result in hyperkalemia.	189,190
Captopril-spironolactone	1	1	May result in hyperkalemia.	189,190
Clopidogrel-esomeprazole	1	39	May result in reduced plasma concentrations of clopidogrel active metabolite.	138,139
Amlodipine-clopidogrel	1	3	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Amiodarone-carvedilol	1	1	Hypotension, bradycardia, or cardiac arrest.	244
Co-amoxiclav-warfarin	1	1	Increased risk of bleeding.	134
Amoxicillin-warfarin	1	1	Increased risk of bleeding.	134
Digoxin-spironolactone	1	8	May result in increased digoxin exposure.	245
Aspirin-warfarin	1	2	Increased risk of bleeding.	22,23
Clopidogrel-diltiazem	1	8	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208

Atorvastatin-clarithromycin	1	1	Increased atorvastatin exposure and an increased risk of myopathy or rhabdomyolysis.	[130,131]
Atorvastatin-diltiazem	1	8	Increased risk of rhabdomyolysis.	[256,257]
Carvedilol-verapamil	1	1	May result in hypotension, bradycardia.	[258]
Digoxin-hydrochlorothiazide	1	1	Digitalis toxicity (nausea, vomiting, arrhythmias).	[259]
Diltiazem-metoprolol	1	1	Increased risk of hypotension, bradycardia, AV conduction disturbances.	[260]
Glimepiride-levofloxacin	1	1	Changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.	[261]
Lisinopril-spironolactone	1	1	May result in hyperkalemia.	[189,190]
Losartan-ramipril	1	1	Increased risk of adverse events (i.e., hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure).	[262]
Propranolol-verapamil	1	1	May result in hypotension, bradycardia.	[263]
Aspirin-dexamethasone	2	4	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[142,115]
Aspirin-metoprolol	2	84	May result in decreased antihypertensive effect.	[165]
Aspirin-nitroglycerin	2	97	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	[124,125]

Furosemide-lisinopril	2	3	May result in postural hypotension (first dose).	151
Furosemide-ramipril	2	33	May result in postural hypotension (first dose).	151
Furosemide-captopril	2	6	May result in postural hypotension (first doe).	151
Aspirin-furosemide	2	57	May result in decreased diuretic and antihypertensive efficacy.	121,122
Aspirin-spironolactone	2	14	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.	123
Aspirin-carvedilol	2	24	May result in decreased antihypertensive effect.	124,125
Aspirin-bisoprolol	2	18	May result in decreased antihypertensive effect.	124,125
Aspirin-losartan	2	23	May result in decreased antihypertensive effects and an increased risk of renal impairment.	127
Aspirin-valsartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	127
Aspirin-candesartan	2	2	May result in decreased antihypertensive effects and an increased risk of renal impairment.	127
Aspirin-irbesartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	127
Aspirin-amlodipine	2	4	Increased risk of gastrointestinal hemorrhage and/or	141
Aspirin-hydrochlorothiazide	2	11	antagonism of hypotensive effect. Decreased diuretic and antihypertensive efficacy.	145
Amlodipine-metoprolol	2	1	May result in hypotension and/or bradycardia.	152,153

Amlodipine-carvedilol	2	1	May result in hypotension and/or bradycardia.	[152,153]
Digoxin-furosemide	2	21	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[213]
Aspirin-diltiazem	2	7	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Aspirin-lisinopril	2	13	May result in decreased lisinopril effectiveness.	[230]
Aspirin-captopril	2	16	May result in decreased captopril effectiveness.	[230]
Aspirin-enalapril	2	1	May result in decreased enalapril effectiveness.	[230]
Aspirin-glimepiride	2	7	Increased risk of hypoglycemia.	[249]
Atorvastatin-digoxin	2	4	Increased plasma concentrations of digoxin.	[250]
Carvedilol-digoxin	2	4	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[251]
Bisoprolol-glimepiride	2	1	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Bisoprolol-metformin	2	2	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Digoxin-metoprolol	2	4	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[232]
Metformin-metoprolol	2	2	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]

Atorvastatin-clopidogrel	2	97	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.	[210]
Carvedilol-glimepiride	2	1	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Aspirin-nifedipine	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Aspirin-verapamil	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Glimepiride-metoprolol	2	3	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Bisoprolol-glyburide	2	1	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[264]
Captopril-digoxin	2	2	Increase in digoxin plasma concentrations.	[265]
Carvedilol-doxazosin	2	1	May result in an exaggerated hypotensive response to the first dose of the alpha blocker.	[266]
Digoxin-omeprazole	2	5	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[166]
Levofloxacin-prednisolone	2	1	Increased risk for tendon rupture.	[267]

3.3.2.6 Association of PDDIs with other parameters in CCU of KTH

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 3 or more drugs (OR = 35.157; 95%CI = 1.041-1187.61; p = 0.047). An insignificant association was found between the presence of PDDIs and duration of stay of 3 or more days (OR = 0.916; 95%CI = 0.108-7.768; p = 0.936), and with gender (OR = 0.325; 95%CI = 0.076-1.384; p = 0.128). The results are shown in Table 3.96.

Table 3.96 logistic regression analysis in CCU of KTH

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=251)	**Interactions absent (n=9)**		
Prescribed drugs				
< 3	1	1		
≥ 3	250	8	35.157 (1.041-1187.61)	0.047
Duration of stay				
< 3	33	2		
≥ 3	218	7	0.916 (0.108-7.768)	0.936
Gender				
Male	151	3		
Female	100	6	0.076 (0.076-1.384)	0.128

3.3.2.7 Drugs used

A total of 81 drugs were prescribed in the CCU of KTH appearing 1500 times in all the medication charts as shown in Table 3.97.

Table 3.97 Frequencies of commonly used drugs in CCU of KTH

Drug Name	Dosage Form	Frequency
Clopidogrel + Aspirin	Tablets	149
Enoxaparin	Subcutaneous	135
Atorvastatin	Tablets	102
Metoprolol	Tablets	94
Ramipril	Tablets	93
Nitroglycerin	Tablets	92
Rosuvastatin	Tablets	87
Aspirin	Tablets	72
Furosemide	Tablets	70
Clopidogrel	Tablets	62
Ceftriaxone	Intravenous	50
Ipratropium	Nebules	36
Esomeprazole	Intravenous	31
Ranitidine	Intravenous	30
Beclomethasone	Nebules	30
Carvedilol	Tablets	30
Digoxin	Tablets	26
Losartan	Tablets	23
Bisoprolol	Tablets	20
Esomeprazole	Tablets	18
Captopril	Tablets	18
Spironolactone	Tablets	15
Trimetazidine	Tablets	15
Lisinopril	Tablets	14
Furosemide+spironolactone	Tablets	13

Isosorbide mononitrate	Tablets	11
Fondaparinux	Subcutaneous	9
Gliclazide	Tablets	9
Diltiazem	Tablets	8
Domperidone	Tablets	8
Co-amoxiclav	Intravenous	7
Losartan+hydrochlorothiazide	Tablets	7
Glimepiride	Tablets	7
Omeprazole	Intravenous	6
Ciprofloxacin	Tablets	6
Dexamethasone	Intravenous	5
Metronidazole	Intravenous	5
Levofloxacin	Tablets	5
Warfarin	Tablets	5
Metformin	Tablets	5
Albuterol	Nebules	4
Omeprazole	Tablets	4
Salmeterol+fluticasone	Inhalation	4
Amiodarone	Tablets	3
Cefixime	Tablets	3
Amlodipine	Tablets	3
Famotidine	Tablets	3
Cetirizine	Tablets	3
Cefoperazone+sulbactam	Intravenous	2
Ciprofloxacin	Intravenous	2
Irbesartan+hydrochlorothiazide	Tablets	2
Ranitidine	Tablets	2
Clarithromycin	Tablets	2
Fexofenadine	Tablets	2
Isosorbide dinitrate	Tablets	2
Nicorandil	Tablets	2
Candesartan	Tablets	2
Pantoprazole	Tablets	2

Famotidine	Syrup	2
Verapamil	Tablets	2
Dimenhydrinate	Intravenous	1
Valsartan+hydrochlorothiazide	Tablets	1
Valsartan	Tablets	1
Prednisolone	Tablets	1
Heparin	Subcutaneous	1
Ceftazidime	Intravenous	1
Nifedipine	Tablets	1
Cefuroxime	Intravenous	1
Propranolol	Tablets	1
Pitavastatin	Tablets	1
Enalapril	Tablets	1
Ipratropium	Inhalation	1
Furosemide+amiloride	Tablets	1
Lisinopril+hydrochlorothiazide	Tablets	1
Co-amoxiclav	Tablets	1
Doxazosin	Tablets	1
Beclomethasone	Inhalation	1
Metronidazole	Tablets	1
Dalterparin	Subcutaneous	1
Amiloride+hydrochlorothiazide	Tablets	1
Glyburide	Tablets	1

3.3.2.8 Indications

Myocardial infarction was the most prevalent indication in the CCU of KTH (515 cases of 1500) followed by hyperlipidemia (190 cases), hypertension (146 cases), angina (134 cases), stress ulcer (92 cases), heart failure (79 cases), secondary infections (73 cases), thrombosis (53 cases), and edema (40 cases), while the rest of the cases were contributed by other indications.

3.3.2.9 Drug class

A total of 22 drug classes were used in the CCU of KTH with antiplatelet being the most prevalent drug class as shown in Table 3.98.

Table 3.98 Frequencies of Drug classes used in CCU of KTH

Drug Class	Frequency
Antiplatelet	283
HMG Co-A reductase inhibitor	190
Anticoagulant	151
Beta blocker	145
ACE inhibitor	127
Nitrates	105
Diuretic	100
Antibacterial	86
Proton Pump Inhibitors	61
Bronchodilator	44
Corticosteroid	38
H2 receptor antagonist	37
ARBs	36
Cardiac glycoside	26
Anti ischemic agent	17
Sulfonyl ureas	16
Calcium channel blocker	14
Antiemetic	9
H1 receptor antagonist	5
Biguanides	5
Antiarrhythmic	3
Adrenergic blocker	1

3.3.2.10 Dosing errors in CCU of KTH

Out of the total 1499 cases, 195 (13.0%) had subtherapeutic doses while 15 (1.0%) had overdoses as shown in Table 3.99 and Table 3.100 respectively.

Table 3.99 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Nitroglycerin	Tablets	92
Ranitidine	Intravenous	27
Ramipril	Tablets	18
Carvedilol	Tablets	12
Captopril	Tablets	9
Metoprolol	Tablets	8
Diltiazem	Tablets	6
Isosorbide mononitrate	Tablets	3
Diltiazem	Tablets	2
Beclomethasone	Nebules	2
Ipratropium	Nebules	2
Ranitidine	Tablets	1
Valsartan	Tablets	1
Losartan	Tablets	1
Fexofenadine	Tablets	1
Trimetazidine	Tablets	1
Domperidone	Tablets	1
Omeprazole	Intravenous	1
Ceftazidime	Intravenous	1
Co-amoxiclav	Intravenous	1
Lisinopril	Tablets	1
Verapamil	Tablets	1
Enalapril	Tablets	1
Bisoprolol	Tablets	1
Salmeterol + Fluticasone	Inhaler	1

Table 3.100 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Beclomethasone	Nebules	5
Esomeprazole	Intravenous	2
Metoprolol	Tablets	2
Isosorbide mononitrate	Tablets	2
Nifedipine	Tablets	1
Esomeprazole	Tablets	1
Heparin	Subcutaneous	1
Salemeterol+Fluticasone	Inhaler	1

3.3.3 Hayatabad Medical Complex (HMC)

3.3.3.1 General Patient Characteristics

A total of 260 patients were analyzed in the CCU of HMC, of which 143 (55.0%) were males and 117 (45.0%) were females. The mean age of the population was 58.82 years and ranged from 18 to 90 years. Of the total patients, 45.4% were between the ages of 19 to 59 years, 0.8% were of 18 years and below, while 53.8% patients were of 60 years and above. Mean duration of stay in the critical care unit was 2.75 ± (1.11) days and the mean number of prescribed drugs were 6.28 ± (7.82) as shown in Table 3.101.

The top three leading causes of admission in the CCU or HMC were myocardial infarction, acute coronary syndrome and heart failure as shown in Figure 3.11.

Table 3.101 General Patient Characteristics in CCU of HMC

Variables	**Frequency (%)**
Gender	
Male	143 (55.0%)
Female	117 (45.0%)
Age (years)	
Mean ± SD	58.82 (± 12.75)
Median	60
Range	18-90
≤ 18	2 (0.8%)
19-59	118 (45.4%)
≥ 60	140 (53.8%)
Drugs prescribed per patient	
Mean ± SD	6.28 ± (7.82)
Median	6
Range	2-12
≤ 4	34 (13.1%)
5-6	128 (49.2%)
≥ 7	98 (37.7%)
Stay in ICU (days)	
Mean ± SD	2.75 ± (1.11)
Median	2
Range	2-8
≤ 2	145 (55.7%)
3-5	99 (38.1%)
≥ 6	16 (6.2%)

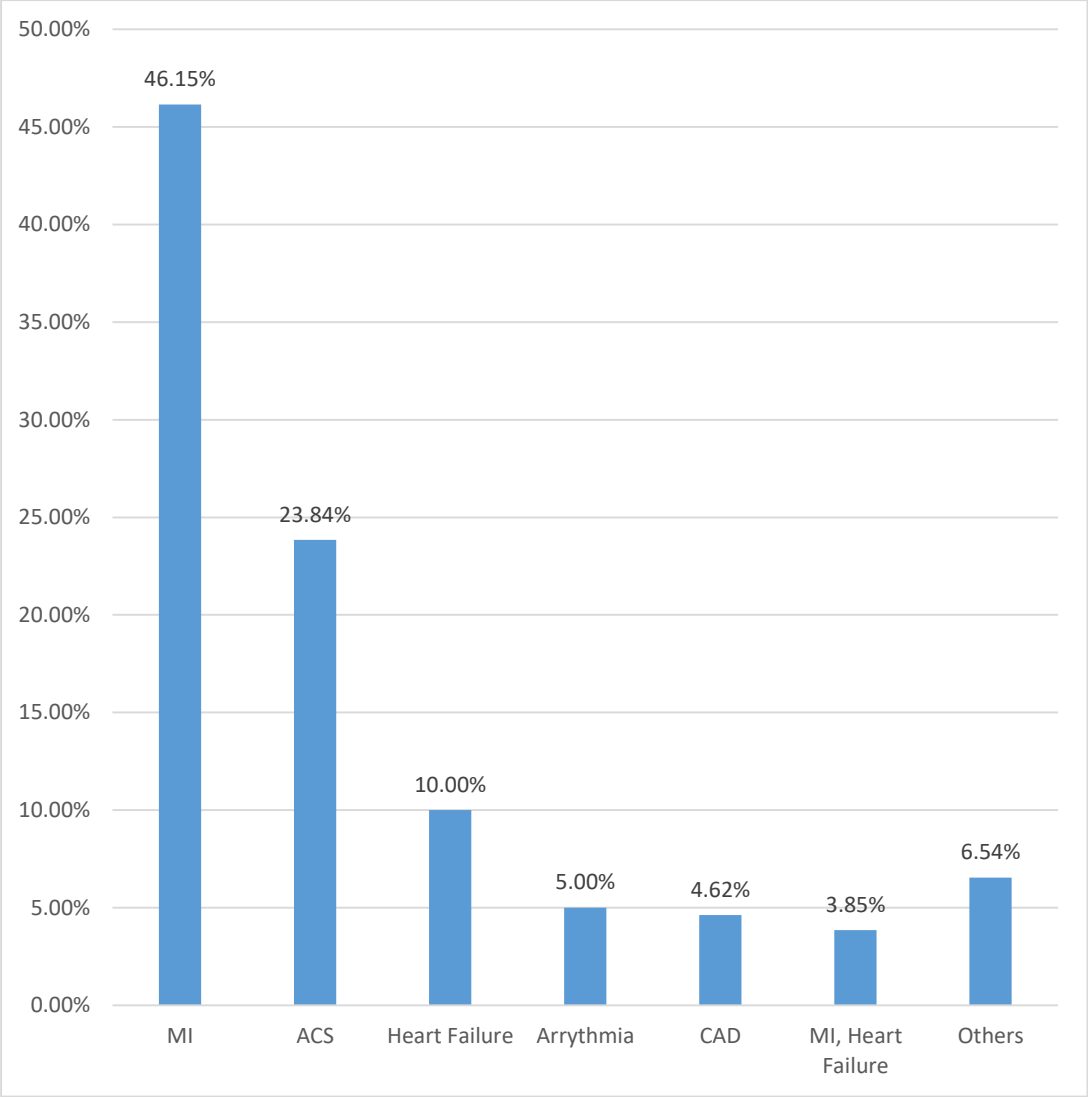

Figure 3.11 Causes of admission to CCU of HMC

3.3.3.2 Prevalence of Potential drug-drug interactions

A prevalence of 95.8% PDDIs was reported in the patients of CCU of HMC. Fifty seven patients had 6 PDDIs while fifty five patients had 5 PDDIs. The prevalence of PDDIs is shown in Table 3.102.

Table 3.102 Prevalence of PDDIs in CCU of HMC

No. of PDDIs	Frequency	Percentage %
1	19	7.3
2	22	8.5
3	14	5.4
4	19	7.3
5	55	21.2
6	57	21.9
7	28	10.8
8	13	5.0
9	17	6.5
10	1	0.4
11	3	1.2
13	1	0.4

3.3.3.3 Categories of PDDIs

The PDDIs reported in the CCU of HMC were classified on the basis of severity, documentation, onset and clinical significance. The type and mechanisms of interactions were also identified. A total of 93 interacting drug pairs were identified which caused 1253 drug-drug interactions. The severity of 45.6% PDDIs were major, 54% were moderate while 0.4% were of minor severity. Documentation of 38% PDDIs were fair, 51.2% of the PDDIs were of good and 10.8% of the PDDIs were of excellent documentation. On the basis of onset of PDDIs, 56.2% were of unknown onset, 23% PDDIs were of rapid onset and 20.8% were of delayed onset. Pharmacokinetic interactions were present in 27.1% PDDIs, 71.6% PDDIs were of pharmacodynamics type while 1.3% PDDIs were of unknown type. In terms of mechanism, synergism contributed in 45.6% PDDIs, antagonism was involved in 26% PDDIs, absorption contributed to 0.2% PDDIs, metabolism contributed for 9.3% PDDIs, elimination contributed in 17.5% PDDIs, combination of absorption and metabolism contributed in 0.1% PDDIs, while 1.3% PDDIs were of unknown mechanism as shown in Table 3.103.

Table 3.103 Categories of PDDIs in CCU of HMC

Variable	Frequency (%)
Severity of PDDIs	
Major	572 (45.6%)
Moderate	676 (54%)
Minor	5 (0.4%)
Documentation of PDDIs	
Excellent	136 (10.8%)
Good	641 (51.2%)
Fair	476 (38%)
Onset of PDDIs	
Rapid	288 (23%)
Delayed	261 (20.8%)
Unknown	704 (56.2%)
Type of Interaction	
Pharmacodynamic	898 (71.6%)
Pharmacokinetic	339 (27.1%)
Unknown	16 (1.3%)
Mechanism of Interaction	
Synergism	572 (45.6%)
Antagonism	326 (26%)
Absorption	2 (0.2%)
Metabolism	117 (9.3%)
Elimination	219 (17.5%)
Absorption/Metabolism	1 (0.1%)
Unknown	16 (1.3%)

3.3.3.4 Interacting Drug Pairs

In the CCU of HMC, 93 interacting drug pairs were identified causing 1253 drug-drug interactions, of these interacting drug pairs, 7 were involved in 818 (65.2%) interactions of which 3 were major and 4 were moderate as shown in Table 3.104.

Table 3.104 Interacting drug pairs in the CCU of HMC

Interacting Pair	Frequency	Percentage
aspirin-clopidogrel	183	14.6%
clopidogrel-enoxaparin	143	11.4%
aspirin-enoxaparin	138	11.0%
aspirin-nitroglycerin	115	9.2%
aspirin-ramipril	103	8.2%
aspirin-bisoprolol	80	6.4%
atorvastatin-clopidogrel	56	4.5%
aspirin-furosemide	54	4.3%
aspirin-metoprolol	46	3.7%
ramipril-furosemide	31	2.5%
aspirin-spironolactone	19	1.5%
clopidogrel-omeprazole	16	1.3%
aspirin-captopril	15	1.2%
digoxin-furosemide	14	1.1%
aspirin-lisinopril	14	1.1%
aspirin-candesartan	13	1.0%
clopidogrel-fondaparinux	11	0.9%
aspirin-fondaparinux	11	0.9%
ramipril-spironolactone	11	0.9%
aspirin-valsartan	10	0.8%
aspirin-diltiazem	10	0.8%
digoxin-spironolactone	8	0.6%

aspirin-hydrochlorothiazide	7	0.6%
aspirin-losartan	7	0.6%
clopidogrel-esomeprazole	7	0.6%
aspirin-carvedilol	7	0.6%
clopidogrel-diltiazem	7	0.6%
aspirin-dexamethasone	6	0.5%
captopril-furosemide	5	0.4%
aspirin-glimepiride	5	0.4%
atorvastatin-diltiazem	4	0.3%
amiodarone-bisoprolol	4	0.3%
dexamethasone-moxifloxacin	4	0.3%
spironolactone-valsartan	4	0.3%
losartan-spironolactone	3	0.2%
captopril-spironolactone	3	0.2%
albuterol-metoprolol	3	0.2%
albuterol-digoxin	3	0.2%
aspirin-telmisartan	3	0.2%
enoxaparin-warfarin	2	0.2%
aspirin-ranitidine	2	0.2%
albuterol-bisoprolol	2	0.2%
aspirin-amlodipine	2	0.2%
aspirin-atenolol	2	0.2%
bisoprolol-digoxin	2	0.2%
spironolactone-warfarin	2	0.2%
candesartan-spironolactone	2	0.2%
bisoprolol-metformin	2	0.2%
digoxin-metoprolol	2	0.2%
amiodarone-clopidogrel	2	0.2%
amiodarone-rosuvastatin	2	0.2%
bisoprolol-glimepiride	2	0.2%
carvedilol-glimepiride	2	0.2%

clopidogrel-simvastatin	2	0.2%
bisoprolol-diltiazem	2	0.2%
aspirin-warfarin	1	0.1%
furosemide-metolazone	1	0.1%
amlodipine-clopidogrel	1	0.1%
albuterol-carvedilol	1	0.1%
furosemide-lisinopril	1	0.1%
clarithromycin-digoxin	1	0.1%
amlodipine-bisoprolol	1	0.1%
amlodipine-aspirin	1	0.1%
betamethasone-moxifloxacin	1	0.1%
amlodipine-carvedilol	1	0.1%
clopidogrel-rabeprazole	1	0.1%
bosentan-sildenafil	1	0.1%
digoxin-omeprazole	1	0.1%
ceftriaxone-warfarin	1	0.1%
clopidogrel-verapamil	1	0.1%
aspirin-enalapril	1	0.1%
amiodarone-ciprofloxacin	1	0.1%
salmeterol-moxifloxacin	1	0.1%
carvedilol-metformin	1	0.1%
aspirin-nebivolol	1	0.1%
captopril-digoxin	1	0.1%
furosemide-gentamicin	1	0.1%
amiodarone-metronidazole	1	0.1%
aspirin-levofloxacin	1	0.1%
ranitidine-warfarin	1	0.1%
aspirin-verapamil	1	0.1%
clarithromycin-rosuvastatin	1	0.1%
diltiazem-metoprolol	1	0.1%
metformin-metoprolol	1	0.1%

captopril-losartan	1	0.1%
clarithromcyin-dexamethasone	1	0.1%
amiodarone-verapamil	1	0.1%
amlodipine-diltiazem	1	0.1%
metformin-moxifloxacin	1	0.1%
glimepiride-moxifloxacin	1	0.1%
metformin-nebivolol	1	0.1%
aspirin-metolazone	1	0.1%
metolazone-ramipril	1	0.1%

3.3.3.5 Clinical importance of PDDIs in CCU of HMC

Analysis of the drug interacting pairs for clinical significance yielded 71 pairs having a clinical significance of 1 and 2. These pairs contributed to 61.6% of the total PDDIs (773 of 1253), 22 of which were of clinical significance 1 while 49 were of clinical significance 2. The clinically significant drug interacting pairs along with their potential outcomes are shown in Table 3.105.

Table 3.105 Clinically important interacting pairs and their potential outcomes in CCU of HMC

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Aspirin-enoxaparin	1	138	Increased risk of bleeding.	105,106
Clopidogrel-omeprazole	1	16	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	136,137
Ramipril-spironolactone	1	11	May result in hyperkalemia.	189,190
Captopril-spironolactone	1	3	May result in hyperkalemia.	189,190
Clopidogrel-esomeprazole	1	7	May result in reduced plasma concentrations of clopidogrel active metabolite.	138,139
Amlodipine-clopidogrel	1	1	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Amiodarone-bisoprolol	1	4	Hypotension, bradycardia, or cardiac arrest.	244
Digoxin-spironolactone	1	8	May result in increased digoxin exposure.	245
Aspirin-warfarin	1	1	Increased risk of bleeding.	22,23
Clopidogrel-diltiazem	1	7	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Atorvastatin-diltiazem	1	4	Increased risk of rhabdomyolysis.	256,257

Diltiazem-metoprolol	1	1	Increased risk of hypotension, bradycardia, AV conduction disturbances.	[260]
Glimepiride-moxifloxacin	1	1	Changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.	[261]
Losartan-captopril	1	1	Increased risk of adverse events (i.e., hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure).	[262]
Clarithromycin-digoxin	1	1	May result in digoxin toxicity (nausea, vomiting, arrhythmias).	[223,224]
Clopidogrel-rabeprazole	1	1	May result in increased risk for thrombosis.	[139,241]
Furosemide-metolazone	1	1	May result in increased risk of electrolyte and fluid imbalance.	[227]
Furosemide-gentamicin	1	1	Increased gentamicin plasma and tissue concentrations and additive ototoxicity and/or nephrotoxicity.	[246]
Amiodarone-metronidazole	1	1	Increased risk of QT prolongation.	[268]
Amiodarone-verapamil	1	1	Bradycardia, atrioventricular block and/or sinus arrest.	[269]

Bisoprolol-diltiazem	1	2	Increased risk of hypotension, bradycardia, AV conduction disturbances.	[270]
Metformin-moxifloxacin	1	1	Changes in blood glucose and increased risk of hypoglycemia or hyperglycemia.	[271]
Aspirin-dexamethasone	2	6	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	[142,115]
Aspirin-metoprolol	2	46	May result in decreased antihypertensive effect.	[165]
Aspirin-nitroglycerin	2	115	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	[124,125]
Furosemide-lisinopril	2	1	May result in postural hypotension (first dose).	[151]
Furosemide-ramipril	2	31	May result in postural hypotension (first dose).	[151]
Furosemide-captopril	2	5	May result in postural hypotension (first doe).	[151]
Aspirin-furosemide	2	54	May result in decreased diuretic and antihypertensive efficacy.	[121,122]
Aspirin-spironolactone	2	19	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.	[123]
Aspirin-carvedilol	2	7	May result in decreased antihypertensive effect.	[124,125]
Aspirin-bisoprolol	2	80	May result in decreased antihypertensive effect.	[124,125]

Aspirin-losartan	2	7	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-valsartan	2	10	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-candesartan	2	13	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-telmisartan	2	3	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-amlodipine	2	3	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[141]
Aspirin-hydrochlorothiazide	2	7	Decreased diuretic and antihypertensive efficacy.	[145]
Amlodipine-bisoprolol	2	1	May result in hypotension and/or bradycardia.	[152,153]
Amlodipine-carvedilol	2	1	May result in hypotension and/or bradycardia.	[152,153]
Digoxin-furosemide	2	14	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[213]
Aspirin-diltiazem	2	10	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Aspirin-lisinopril	2	14	May result in decreased lisinopril effectiveness.	[230]
Aspirin-captopril	2	15	May result in decreased captopril effectiveness.	[230]

Aspirin-enalapril	2	1	May result in decreased enalapril effectiveness.	[230]
Aspirin-glimepiride	2	5	Increased risk of hypoglycemia.	[249]
Bisoprolol-digoxin	2	2	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[251]
Bisoprolol-glimepiride	2	2	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Bisoprolol-metformin	2	2	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Digoxin-metoprolol	2	2	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[232]
Metformin-metoprolol	2	1	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Atorvastatin-clopidogrel	2	56	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.	[210]
Carvedilol-glimepiride	2	2	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Aspirin-verapamil	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Captopril-digoxin	2	1	Increase in digoxin plasma concentrations.	[265]

Digoxin-omeprazole	2	1	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[166]
Carvedilol-metformin	2	1	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Metformin-nebivolol	2	1	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Bisoprolol-digoxin	2	2	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[232]
Ceftriaxone-warfarin	2	1	Increased risk of bleeding.	[158]
Dexamethasone-moxifloxacin	2	4	Increased risk of tendon rupture.	[165]
Betamethasone-moxifloxacin	2	1	Increased risk of tendon rupture.	[165]
Aspirin-atenolol	2	2	May result in decreased antihypertensive effect.	[124,125]
Aspirin-nebivolol	2	1	May result in decreased antihypertensive effect.	[124,125]
Amlodipine-diltiazem	2	1	Increased amlodipine concentrations.	[229]
Amiodarone-clopidogrel	2	2	Ineffective inhibition of platelet aggregation.	[188]
Aspirin-metolazone	2	1	Decreased diuretic and antihypertensive efficacy.	[145]
Bosentan-sildenafil	2	1	Increased bosentan plasma concentrations and decreased sildenafil plasma concentrations	[272]

Clopidogrel-simvastatin	2	2	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.	[210]
Metolazone-ramipril	2	1	Postural hypotension (first dose).	[273]
Amiodarone-rosuvastatin	2	2	May result in elevations in serum transaminase levels.	[247]

3.3.3.6 Association of PDDIs with other parameters in CCU of HMC

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 6 or more drugs (OR = 12.756; 95%CI = 2.637-61.706; p = 0.002). An insignificant association was found between the presence of PDDIs and duration of stay of 3 or more days (OR = 1.327; 95%CI = 0.364-4.831; p = 0.668), and with gender (OR = 0.658; 95%CI = 0.185-2.339; p = 0.517). The results are shown in Table 3.106.

Table 3.106 logistic regression analysis in CCU of HMC

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=249)	**Interactions absent (n=11)**		
Prescribed drugs				
< 6	68	9		
≥ 6	181	2	12.756 (2.637-61.706)	0.002
Duration of stay				
< 3	138	7		
≥ 3	111	4	1.327 (0.364-4.831)	0.668
Gender				
Male	137	6		
Female	112	5	0.658 (0.185-2.339)	0.517

3.3.3.7 Drugs used

A total of 85 drugs were prescribed in the CCU of HMC appearing 1632 times in all the medication charts as shown in Table 3.107.

Table 3.107 Frequencies of commonly used drugs in CCU of HMC

Drug Name	Dosage Form	Frequency
Enoxaparin	Subcutaneous	159
Nitroglycerin	Tablets	136
Rosuvastatin	Tablets	135
Ramipril	Tablets	120
Aspirin	Tablets	115
Clopidogrel	Tablets	104
Clopidogrel + Aspirin	Tablets	102
Bisoprolol	Tablets	100
Furosemide	Intravenous	65
Ceftriaxone	Intravenous	63
Atorvastatin	Tablets	60
Metoprolol	Tablets	54
Beclomethasone	Nebules	26
Isosorbide mononitrate	Tablets	22
Albuterol	Nebules	21
Spironolactone	Tablets	21
Trimetazidine	Tablets	20
Captopril	Tablets	19
Omeprazole	Intravenous	18
Digoxin	Tablets	15
Lisinopril	Tablets	15
Candesartan	Tablets	14
Fondaparinux	Subcutaneous	13
Nicorandil	Tablets	12
Moxifloxacin	Intravenous	11

Furosemide+spironolactone	Tablets	11
Diltiazem	Tablets	10
Ipratropium	Nebules	10
Carvedilol	Tablets	10
Valsartan	Tablets	9
Moxifloxacin	Tablets	9
Losartan	Tablets	8
Dexamethasone	Intravenous	7
Omeprazole	Tablets	7
Gliclazide	Tablets	7
Valsartan+hydrochlorothiazide	Tablets	6
Amiodarone	Tablets	6
Esomeprazole	Tablets	6
Glimepiride	Tablets	6
Metformin	Tablets	5
Furosemide	Tablets	5
Amlodipine	Tablets	4
Warfarin	Tablets	4
Pantoprazole	Tablets	4
Verapamil	Tablets	4
Telmisartan	Tablets	3
Ranitidine	Intravenous	2
Nebivolol	Tablets	2
Losartan+hydrochlorothiazide	Tablets	2
Metronidazole	Intravenous	2
Atenolol	Tablets	2
Levofloxacin	Tablets	2
Clarithromycin	Tablets	2
Domperidone	Tablets	2
Simvastatin	Tablets	2
Beraprost	Tablets	2
Dexamethasone	Tablets	2
Rabeprazole	Tablets	2

Ciprofloxacin	Intravenous	1
Co-amoxiclav	Intravenous	1
Montelukast	Tablets	1
Esomeprazole	Intravenous	1
Propranolol	Tablets	1
Bosentan	Tablets	1
Lactulose	Syrup	1
Metoclopramide	Intravenous	1
Alfacalcidol	Tablets	1
Pitavastatin	Tablets	1
Enalapril	Tablets	1
Sucralfate	Syrup	1
Salmeterol+fluticasone	Inhalation	1
Carbimazole	Tablets	1
Metolazone	Tablets	1
Potassium chloride	Tablets	1
Gentamicin	Intravenous	1
Metoclopramide	Tablets	1
Famotidine	Tablets	1
Sildenafil	Tablets	1
Co-amoxiclav	Tablets	1
Epoetin alfa	Subcutaneous	1
Candesartan+hydrochlorothiazide	Tablets	1
Glimepiride+metformin	Tablets	1
Betamethasone	Tablets	1
Sulfasalazine	Tablets	1
Gemifloxacin	Tablets	1

3.3.3.8 Indications

Myocardial infarction was the most prevalent indication in the CCU of HMC (536 cases of 1632) followed by hypertension (237 cases), angina (216 cases), hyperlipidemia (198 cases), heart failure (97 cases), secondary infections (66 cases), asthma (59 cases) and thrombosis (43 cases), while the rest of the cases were contributed by other indications.

3.3.3.9 Drug class

A total of 30 drug classes were used in the CCU of HMC with antiplatelet being the most prevalent drug class as shown in Table 3.108.

Table 3.108 Frequencies of Drug classes used in CCU of HMC

Drug Class	Frequency
Antiplatelet	321
HMG Co-A reductase inhibitor	198
Anticoagulant	176
Beta blocker	169
Nitrates	158
ACE inhibitor	155
Diuretic	103
Antibacterial	95
ARBs	43
PPI	38
Corticosteroid	37
Anti ischemic agent	32
Bronchodilator	31
Calcium channel blocker	18
Cardiac glycoside	15
Sulfonyl ureas	13
Antiarrhythmic	6
Biguanides	5
Antiemetic	4
H2 receptor antagonist	3
Nutriceutical	2
Prostacyclin analogue	2
Leukotriene receptor antagonist	1
Antithyroid agent	1
Sulfonyl urea+biguanides	1
Endothelial receptor antagonist	1
Mucosal protective agents	1
Laxative	1
Vasodilator	1
Hematopoietic	1

3.3.3.10 Dosing errors in CCU of HMC

Out of the total 1623 cases, 201 (12.3%) had subtherapeutic doses while 18 (1.1%) had overdoses as shown in Table 3.109 and Table 3.110 respectively.

Table 3.109 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Nitroglycerin	Tablets	130
Ramipril	Tablets	15
Captopril	Tablets	15
Isosorbide mononitrate	Tablets	6
Diltiazem	Tablets	6
Trimetazidine	Tablets	5
Carvedilol	Tablets	4
Valsartan	Tablets	4
Candesartan	Tablets	3
Beraprost	Tablets	2
Verapamil	Tablets	2
Nebivolol	Tablets	2
Ipratropium	Nebules	2
Propranolol	Tablets	1
Metoprolol	Tablets	1
Carbimazole	Tablets	1
Valsartan	Tablets	1
Ranitidine	Intravenous	1

Table 3.110 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Beclomethasone	Nebules	4
Dexamethasone	Intravenous	3
Diltiazem	Tablets	2
Metoprolol	Tablets	2
Isosorbide mononitrate	Tablets	1
Dexamethasone	Tablets	1
Furosemide	Intravenous	1
Bisoprolol	Tablets	1
Spironolactone	Tablets	1
Sildenafil	Tablets	1
sucralfate	Syrup	1

3.3.4 Northwest General Hospital & Research Center (NWGH & RC)

3.3.4.1 General Patient Characteristics

In CCU of NWGH & RC, 250 patients were analyzed, of which 148 (59.2%) were males and 102 (40.8%) were females. The mean age of the population was 58.06 years and ranged from 19 to 88 years. A total of 50.8% patients were between the ages of 19 to 59 years, while 15.2% were of 18 years and below. Mean duration of stay in the critical care unit was 3.62 ± (1.78) days and the mean number of prescribed drugs were 5.81 ± (1.94) as shown in Table 3.111.

The top three leading causes of admission in the CCU of NWGH & RC were myocardial infarction, acute coronary syndrome and heart failure as shown in Figure 3.12.

Table 3.111 General Characteristics of Patients in CCU of NWGH & RC

Variables	**Frequency (%)**
Gender	
Male	148 (59.2%)
Female	102 (40.8%)
Age (years)	
Mean ± SD	58.06 (± 12.75)
Median	58
Range	19-88
19-59	127 (50.8%)
≥ 60	123 (49.2%)
Drugs prescribed per patient	
Mean ± SD	5.81 ± (1.94)
Median	5
Range	2-13
≤ 4	56 (22.4%)
5-6	113 (45.2%)
≥ 7	81 (32.4%)
Stay in ICU (days)	
Mean ± SD	3.62 ± (1.78)
Median	3
Range	1-16
≤ 2	74 (29.6%)
3-5	118 (47.2%)
≥ 6	58 (23.2%)

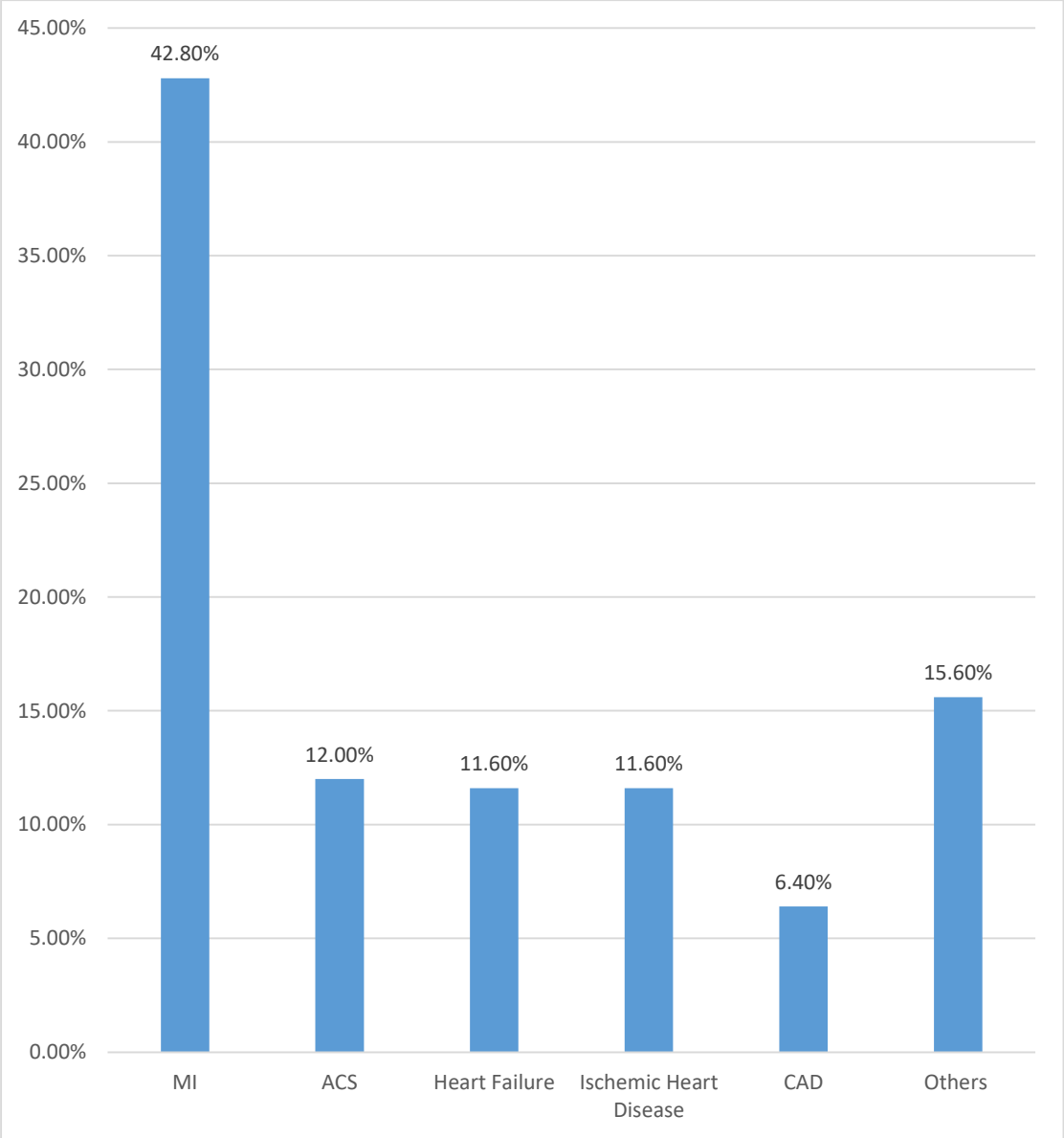

Figure 3.12 Causes of admission to CCU of NWGH & RC

3.3.4.2 Prevalence of Potential drug-drug interactions

The prevalence of PDDIs in patients of CCU of NWGH & RC was reported to be 92%. Of the total 250 patients, fifty seven had 2 PDDIs while one patient had 14 PDDIs. The prevalence of PDDIs is shown in Table 3.112.

Table 3.112 Prevalence of PDDIs in CCU of NWGH & RC

No. of PDDIs	Frequency	Percentage %
1	18	7.2
2	57	22.8
3	47	18.8
4	30	12.0
5	32	12.8
6	16	6.4
7	14	5.6
8	4	1.6
10	7	2.8
11	2	0.8
12	2	0.8
14	1	0.4

3.3.4.3 Categories of PDDIs

The PDDIs reported in the CCU of NWGH & RC were classified on the basis of severity, documentation, onset and clinical significance. The type and mechanisms of interactions were also identified. A total of 105 interacting drug pairs were identified which caused 909 drug-drug interactions. According to severity 41.4% of the PDDIs were of major, 54.6% were of moderate, while the percentage of minor severity PDDIs was 4% each. Fairly documented PDDIs were 38.6%, 52.7% were of good documentation and 8.7% were of excellent documentation. The onset of 55.8% PDDIs was unknown while 14.8% PDDIs were of rapid and 29.4% were of delayed onset. According to type of interactions, 74.3% PDDIs were of pharmacodynamics type and 23.2% PDDIs were of pharmacokinetic type while 2.5% were of unknown type. In terms of mechanism 42.1% PDDIs were due to synergism, 32.2% were due to antagonism, 3.2% PDDIs were due to absorption, 7.6% PDDIs were due to metabolism, 12.2% PDDIs were due to elimination, 0.2% PDDIs were due to combined effect of absorption and metabolism, and 2.5% were of unknown mechanisms as shown in Table 3.113.

Table 3.113 Categories of PDDIs in CCU of NWGH & RC

Variable	**Frequency (%)**
Severity of PDDIs	
Major	377 (41.4%)
Moderate	496 (54.6%)
Minor	36 (4.0%)
Documentation of PDDIs	
Excellent	79 (8.7%)
Good	479 (52.7%)
Fair	351 (38.6%)
Onset of PDDIs	
Rapid	135 (14.8%)
Delayed	267 (29.4%)
Unkonwn	507 (55.8%)
Type of Interaction	
Pharmacodynamic	675 (74.3%)
Pharmacokinetic	211 (23.2%)
Unknown	23 (2.5%)
Mechanism of Interaction	
Synergism	383 (42.1%)
Antagonism	292 (32.2%)
Absorpiton	29 (3.2%)
Metabolism	69 (7.6%)
Elimination	111 (12.2%)
Absorption/metabolism	2 (0.2%)
Unknown	23 (2.5%)

3.3.4.4 Interacting Drug Pairs

In the CCU of NWGH & RC, 105 interacting drug pairs were identified causing 909 drug-drug interactions, of these interacting drug pairs, 6 were involved in 499 (54.9%) interactions of which 3 were major and 3 were moderate in severity as shown in Table 3.114.

Table 3.114 Interacting drug pairs in CCU of NWGH & RC

Interacting Pair	Frequency	Percentage
aspirin-clopidogrel	178	19.6%
aspirin-ramipril	73	8.0%
clopidogrel-enoxaparin	65	7.2%
aspirin-enoxaparin	64	7.0%
aspirin-furosemide	61	6.7%
aspirin-bisoprolol	58	6.4%
aspirin-metoprolol	31	3.4%
aspirin-ranitidine	27	3.0%
atorvastatin-clopidogrel	25	2.8%
ramipril-furosemide	22	2.4%
aspirin-carvedilol	20	2.2%
aspirin-spironolactone	19	2.1%
aspirin-nitroglycerin	18	2.0%
aspirin-glimepiride	18	2.0%
aspirin-valsartan	16	1.8%
digoxin-furosemide	11	1.2%
aspirin-hydrochlorothiazide	11	1.2%
aspirin-losartan	11	1.2%
ramipril-spironolactone	10	1.1%
bisoprolol-glimepiride	8	0.9%
clopidogrel-omeprazole	7	0.8%

clopidogrel-rabeprazole	7	0.8%
aspirin-atenolol	6	0.7%
aspirin-irbesartan	6	0.7%
aspirin-lisinopril	4	0.4%
aspirin-amiloride	4	0.4%
aspirin-hydrocortisone	4	0.4%
amlodipine-clopidogrel	3	0.3%
enoxaparin-naproxen	3	0.3%
amlodipine-aspirin	3	0.3%
bisoprolol-digoxin	3	0.3%
digoxin-omeprazole	3	0.3%
naproxen-ramipril	3	0.3%
carvedilol-metformin	3	0.3%
gemfibrozil-rosuvastatin	3	0.3%
aspirin-chlorthalidone	3	0.3%
carvedilol-glimepiride	3	0.3%
irbesartan-spironolactone	3	0.3%
hydrocortisone-moxifloxacin	2	0.2%
enoxaparin-warfarin	2	0.2%
diclofenac+misoprostol-valsartan	2	0.2%
artemether-quinine	2	0.2%
amiloride-aspirin	2	0.2%
digoxin-spironolactone	2	0.2%
spironolactone-valsartan	2	0.2%
amlodipine-carvedilol	2	0.2%
albuterol-metoprolol	2	0.2%
ciprofloxacin-metronidazole	2	0.2%
amlodipine-atenolol	2	0.2%
furosemide-hydrocortisone	2	0.2%
diclofenac+misoprostol-hydrochlorothiazide	2	0.2%
digoxin-tramadol	2	0.2%

atenolol-albuterol	2	0.2%
aspirin-fluoxetine	2	0.2%
aspirin-levofloxacin	2	0.2%
carvedilol-digoxin	2	0.2%
carvedilol-dobutamine	2	0.2%
clopidogrel-fluoxetine	2	0.2%
metformin-metoprolol	2	0.2%
ciprofloxacin-metoprolol	2	0.2%
glimepiride-metoprolol	2	0.2%
enoxaparin-fluoxetine	2	0.2%
amiloride-ramipril	2	0.2%
aspirin-warfarin	1	0.1%
amiloride-digoxin	1	0.1%
digoxin-metoclopramide	1	0.1%
clarithromycin-moxifloxacin	1	0.1%
albuterol-bisoprolol	1	0.1%
aspirin-amlodipine	1	0.1%
albuterol-carvedilol	1	0.1%
captopril-spironolactone	1	0.1%
captopril-furosemide	1	0.1%
aspirin-candesartan	1	0.1%
spironolactone-warfarin	1	0.1%
bisoprolol-metformin	1	0.1%
aspirin-captopril	1	0.1%
clopidogrel-esomeprazole	1	0.1%
digoxin-metoprolol	1	0.1%
clarithromycin-dexamethasone	1	0.1%
aspirin-dexamethasone	1	0.1%
clarithromycin-fluticasone	1	0.1%
levofloxacin-metronidazole	1	0.1%
bosentan-sildenafil	1	0.1%

ceftriaxone-warfarin	1	0.1%
clarithromycin-sulfamethoxazole	1	0.1%
clopidogrel-verapamil	1	0.1%
albuterol-digoxin	1	0.1%
doxazosin-metoprolol	1	0.1%
clarithromycin-salmeterol	1	0.1%
furosemide-sildenafil	1	0.1%
aspirin-diltiazem	1	0.1%
omeprazole-warfarin	1	0.1%
enoxaparin-mefenamic acid	1	0.1%
clopidogrel-diltiazem	1	0.1%
losartan-ramipril	1	0.1%
metoprolol-ranitidine	1	0.1%
warfarin-tramadol	1	0.1%
aspirin-olmesartan	1	0.1%
aspirin-verapamil	1	0.1%
co-amixiclav-warfarin	1	0.1%
diltiazem-metoprolol	1	0.1%
tramadol-warfarin	1	0.1%
amlodipine-diltiazem	1	0.1%
chlorthalidone-ramipril	1	0.1%
amlodipine-metoprolol	1	0.1%

3.3.4.5 Clinical importance of PDDIs in CCU of NWGH & RC

Clinically significant PDDIs were identified using the predetermined criterion and analysis resulted in the identification of 71 interacting pairs which were of clinical significance 1 and 2. These 71 pairs contributed to 57.2% of the total potential drug-drug interactions (520 of 909), of which 18 were of clinically significance 1 while 53 were of clinical significance 2. These clinically significant PDDIs along with their potential outcomes are shown in Table 3.115.

Table 3.115 Clinically important interacting pairs and their potential outcomes in CCU of NWGH & RC

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Aspirin-enoxaparin	1	64	Increased risk of bleeding.	105,106
Clopidogrel-omeprazole	1	7	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	136,137
Ramipril-spironolactone	1	10	May result in hyperkalemia.	189,190
Captopril-spironolactone	1	1	May result in hyperkalemia.	189,190
Clopidogrel-esomeprazole	1	1	May result in reduced plasma concentrations of clopidogrel active metabolite.	138,139
Amlodipine-clopidogrel	1	3	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Digoxin-spironolactone	1	2	May result in increased digoxin exposure.	245
Aspirin-warfarin	1	1	Increased risk of bleeding.	22,23
Clopidogrel-diltiazem	1	1	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Diltiazem-metoprolol	1	1	Increased risk of hypotension, bradycardia, AV conduction disturbances.	260

Losartan-ramipril	1	1	Increased risk of adverse events (i.e., hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure).	262
Clopidogrel-rabeprazole	1	7	May result in increased risk for thrombosis.	139,241
Co-amoxiclave-warfarin	1	1	Increased risk of bleeding.	134
Aspirin-fluoxetine	1	2	Increased risk of bleeding.	274
Enoxaparin-fluoxetine	1	2	Increased risk of bleeding.	275
Enoxaparin-mefenamic acid	1	1	Increased risk of bleeding.	103
Enoxaparin-naproxen	1	3	Increased risk of bleeding.	103
Amiloride-ramipril	1	2	May result in hyperkalemia.	189
Aspirin-dexamethasone	2	1	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	142,115
Aspirin-metoprolol	2	31	May result in decreased antihypertensive effect.	165
Aspirin-nitroglycerin	2	14	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	124,125
Furosemide-ramipril	2	22	May result in postural hypotension (first dose).	151
Furosemide-captopril	2	1	May result in postural hypotension (first doe).	151
Aspirin-furosemide	2	57	May result in decreased diuretic and antihypertensive efficacy.	121,122

Aspirin-spironolactone	2	23	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.	[123]
Aspirin-carvedilol	2	20	May result in decreased antihypertensive effect.	[124,125]
Aspirin-bisoprolol	2	58	May result in decreased antihypertensive effect.	[124,125]
Aspirin-losartan	2	11	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-valsartan	2	16	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-candesartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-olmisartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-irbesartan	2	6	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-amlodipine	2	4	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[141]
Aspirin-hydrochlorothiazide	2	11	Decreased diuretic and antihypertensive efficacy.	[145]
Amlodipine-metoprolol	2	1	May result in hypotension and/or bradycardia.	[152,153]
Amlodipine-carvedilol	2	2	May result in hypotension and/or bradycardia.	[152,153]

Digoxin-furosemide	2	11	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[213]
Aspirin-diltiazem	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Aspirin-lisinopril	2	4	May result in decreased lisinopril effectiveness.	[230]
Aspirin-captopril	2	1	May result in decreased captopril effectiveness.	[230]
Aspirin-glimepiride	2	18	Increased risk of hypoglycemia.	[249]
Bisoprolol-digoxin	2	3	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[251]
Bisoprolol-glimepiride	2	8	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Bisoprolol-metformin	2	1	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Digoxin-metoprolol	2	1	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[232]
Digoxin-carvedilol	2	2	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[232]
Metformin-metoprolol	2	2	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Atorvastatin-clopidogrel	2	25	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.	[210]

Carvedilol-glimepiride	2	3	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Metoprolol-glimepiride	2	2	Hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Aspirin-verapamil	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Digoxin-omeprazole	2	3	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[166]
Carvedilol-metformin	2	3	May result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.	[252]
Ceftriaxone-warfarin	2	1	Increased risk of bleeding.	[158]
Hydrocortisone-moxifloxacin	2	4	Increased risk of tendon rupture.	[165]
Aspirin-atenolol	2	6	May result in decreased antihypertensive effect.	[124,125]
Amlodipine-diltiazem	2	1	Increased amlodipine concentrations.	[229]
Aspirin-chlorthalidone	2	3	Decreased diuretic and antihypertensive efficacy.	[145]
Bosentan-sildenafil	2	1	Increased bosentan plasma concentrations and decreased sildenafil plasma concentrations	[272]
Chlorthalidone-ramipril	2	1	Postural hypotension (first dose).	[273]
Digoxin-tramadol	2	2	Increased risk of digoxin toxicity (nausea, vomiting, cardiac arrhythmias).	[276]

Omeprazole-warfarin	2	1	May result in elevations of INR serum values and potentiation of anticoagulant effects.	[157]
Tramadol-warfarin	2	2	Increase in prothrombin time and an increased risk of bleeding.	[147]
Amiloride-aspirin	2	6	Reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.	[145]
Digoxin-metoclopramide	2	1	May result in decreased digoxin levels.	[172]
Carvedilol-dobutamine	2	2	May result in decreased dobutamine efficacy.	[231]
Amlodipine-atenolol	2	2	May result in hypotension and/or bradycardia.	[277]
Diclofenac-hydrochlorothiazide	2	2	May result in decreased diuretic and antihypertensive efficacy.	[145]
Diclofenac-valsartan	2	2	Decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Doxazosin-metoprolol	2	1	Exaggerated hypotensive response to the first dose of the alpha blocker.	[266]
Naproxen-ramipril	2	3	May result in renal dysfunction or decreased antihypertensive efficacy.	[164]

3.3.4.6 Association of PDDIs with other parameters in CCU of NWGH & RC

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 5 or more drugs (OR = 12.270; 95%CI = 4.297-35.035; p = 0.000). An insignificant association was found between the presence of PDDIs and duration of stay of 3 or more days (OR = 0.477; 95%CI = 0.152-1.496; p = 0.204), and with gender (OR = 2.513; 95%CI = 0.827-7.635; p = 0.104). The results are shown in Table 3.116.

Table 3.116 logistic regression analysis in CCU of NWGH & RC

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=81)	**Interactions absent (n=129)**		
Prescribed drugs				
< 5	2	55		
≥ 5	79	74	12.270 (4.297-35.035)	0.000
Duration of stay				
< 3	28	53		
≥ 3	53	76	0.477 (0.152-1.496)	0.204
Gender				
Male	62	87		
Female	19	42	2.513 (0.827-7.635)	0.104

3.3.4.7 Drugs used

A total of 102 drugs were prescribed in the CCU of NWGH & RC appearing 1452 times in all the medication charts as shown in Table 3.117.

Table 3.117 Frequencies of commonly used drugs in CCU of NWGH & RC

Drug Name	Dosage Form	Frequency
Rosuvastatin	Tablets	165
Aspirin	Tablets	161
Clopidogrel	Tablets	147
Ramipril	Tablets	83
Isosorbide mononitrate	Tablets	76
Enoxaparin	Subcutaneous	74
Bisoprolol	Tablets	67
Furosemide	Intravenous	61
Ceftriaxone	Intravenous	47
Clopidogrel + Aspirin	Tablets	44
Metoprolol	Tablets	33
Ranitidine	Intravenous	31
Carvedilol	Tablets	30
Atorvastatin	Tablets	28
Albuterol	Nebules	26
Nitroglycerin	Tablets	20
Beclomethasone	Nebules	19
Ipratropium	Nebules	19
Pantoprazole	Tablets	18
Spironolactone	Tablets	16
Glimepiride	Tablets	16
Moxifloxacin	Intravenous	15
Valsartan	Tablets	14
Omeprazole	Intravenous	13
Digoxin	Tablets	12

Furosemide+spironolactone	Tablets	9
Losartan	Tablets	9
Metronidazole	Intravenous	8
Co-amoxiclav	Intravenous	7
Ceftazidime	Intravenous	7
Furosemide+amiloride	Tablets	7
Rabeprazole	Tablets	7
Esomeprazole	Intravenous	6
Amlodipine	Tablets	6
Hydrocortisone	Intravenous	6
Dobutamine	Intravenous	6
Valsartan+hydrochlorothiazide	Tablets	5
Irbesartan+hydrochlorothiazide	Tablets	5
Dopamine	Intravenous	5
Tramadol	Intravenous	5
Isosorbide dinitrate	Tablets	5
Ciprofloxacin	Intravenous	4
Dimenhydrinate	Intravenous	4
Warfarin	Tablets	4
Lisinopril	Tablets	4
Nicorandil	Tablets	4
Losartan+hydrochlorothiazide	Tablets	3
Atenolol	Tablets	3
Irbesartan	Tablets	3
Metformin	Tablets	3
Metformin+sitagliptin	Tablets	3
Atenolol+chlorthalidone	Tablets	3
Gemfibrozil	Tablets	3
Naproxen	Tablets	3
Cefoperazone+sulbactam	Intravenous	2
Dexamethasone	Intravenous	2
Piperacillin+tazobactam	Intravenous	2
Clarithromycin	Intravenous	2

Amlodipine+valsartan	Tablets	2
Cefuroxime	Intravenous	2
Metoclopramide	Intravenous	2
Fexofenadine	Tablets	2
Quinine	Intravenous	2
Artemether	Intramuscular	2
Ferrous sulfate+folic acid	Tablets	2
Simvastatin	Tablets	2
Moxifloxacin	Tablets	2
Clonazepam	Tablets	2
Prochlorperazine	Tablets	2
Thyroxine	Tablets	2
Verapamil	Tablets	2
Theophylline	Tablets	2
Diclofenac+misoprostol	Tablets	2
Glimepiride+metformin	Tablets	2
Prasugrel	Tablets	2
Fluoxetine	Tablets	2
Nystatin	Oral drops	1
Montelukast	Tablets	1
Imipenem+cilastatin	Intravenous	1
Diltiazem	Tablets	1
Meropenem	Intravenous	1
Levofloxacin	Tablets	1
Propranolol	Tablets	1
Bosentan	Tablets	1
Lactulose	Syrup	1
Omeprazole	Tablets	1
Clarithromycin	Tablets	1
Folic acid	Tablets	1
Levofloxacin	Intravenous	1
Alfacalcidol	Tablets	1
Captopril	Tablets	1

Candesartan	Tablets	1
Sucralfate	Syrup	1
Salmeterol+fluticasone	Inhalation	1
Metoclopramide	Tablets	1
Sildenafil	Tablets	1
Paracetamol	Tablets	1
Norepinephrine	Intravenous	1
Doxazosin	Tablets	1
Ciprofloxacin	Tablets	1
Olmesartan	Tablets	1
Sulfamethoxazole+trimethoprim	Tablets	1

3.3.4.8 Indications

Myocardial infarction was the most prevalent indication in the CCU of NWGH & RC (384 cases of 1452) followed by hyperlipidemia (198 cases), hypertension (173 cases), angina (116 cases), thrombosis (95 cases), secondary infections (80 cases), stress ulcer (72 cases), asthma (69 cases) and heart failure (58 cases), while the rest of the cases were contributed by other indications.

3.3.4.9 Drug class

A total of 35 drug classes were used in the CCU of NWGH & RC with antibacterial being the most prevalent drug class as shown in Table 3.118.

Table 3.118 Frequencies of Drug classes used in CCU of NWGH & RC

Drug Class	Frequency
Antiplatelet	303
HMG Co-A reductase inhibitor	195
Beta blocker	137
Anticoagulant	129
Antibacterial	105
Nitrates	101
Diuretic	93
ACE inhibitor	88
Bronchodilators	50
ARBs	43
PPI	42
H2 receptor antagonist	31
Corticosteroid	26
Sulfonyl ureas	18
Cardiac glycoside	12
Vasopressor	12
Analgesic	11
Calcium channel blocker	9
Antiemetic	9
Anxiolytic	4
Antimalarial	4
Anti ischemic agent	4
Sulfonyl urea+biguanides	3
Nutriceutical	3
Biguanides	3
Fibric acid antihyperlipidemic	3
Antithyroid agent	2
H1 receptor antagonist	2
Antifungal	1

Endothelial receptor antagonist	1
Antianemic	1
Mucosal protective agents	1
Laxative	1
Vasodilator	1
Adrenergic blocker	1

3.3.4.10 Dosing errors in CCU of NWGH & RC

Out of the total 1449 cases, 89 (6.1%) had subtherapeutic doses while 42 (2.9%) had overdoses as shown in Table 3.119 and 3.120 respectively.

Table 3.119 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Nitroglycerin	Tablets	20
Isosorbide mononitrate	Tablets	11
Ranitidine	Intravenous	9
Bisoprolol	Tablets	7
Carvedilol	Tablets	7
Ceftazidime	Intravenous	5
Isosorbide dinitrate	Tablets	4
Hydrocortisone	Intravenous	4
Co-amoxiclav	Intravenous	3
Naproxen	Tablets	3
Metoprolol	Tablets	2
Ramipril	Tablets	2
Amlodipine	Tablets	2
Piperacillin+Tazobactam	Intravenous	2
Bosentan	Tablets	1
Captopril	Tablets	1
Valsartan	Tablets	1
Levofloxacin	Tablets	1
Diltiazem	Tablets	1
Verapamil	Tablets	1
Ipratropium	Nebules	1
Cefuroxime	Intravenous	1

Table 3.120 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Isosorbide mononitrate	Tablets	15
Albuterol	Nebules	8
Beclomethasone	Nebules	7
Ipratropium	Nebules	3
Clopidogrel	Tablets	2
Pantoprazole	Tablets	2
Furosemide	Intravenous	1
Sildenafil	Tablets	1
Metoprolol	Tablets	1
Sulfamethoxazole+trimethoprim	Tablets	1

3.3.5 Comparison of PDDIs among the hospitals

One-way ANOVA showed a significant difference (p=0.000) in the means of PDDIs among the four hospitals. Post HOC test (LSD) revealed that there was a significant difference (p=0.000) of PDDIs between NWGH & RC and the other three hospitals (LRH, KTH and HMC).

3.3.6 DISCUSSION

Cardiovascular diseases are a prime cause of high mortality rates throughout the world. In 2012, World Health Organization (WHO) estimated that 17.5 million people died worldwide due to cardiovascular diseases. Most of these deaths occurred in low or middle income countries.[278] Risk factors include diseases like hypertension, hyperlipidemia, diabetes or other diseases while behavioral risk factors include unhealthy diet, tobacco use, lack of physical activity and stress.[279,280] Furthermore, treatment for these diseases require multiple drug administration which when combined with factors like advanced age, co-morbidities and changes in hepatic and renal

functions increases the risk of potential drug-drug interactions (PDDIs). Patients in the cardiac intensive care units are prone to even further risk because of their complex physiological and pathological conditions, leading to higher prevalence of PDDIs in such units.

In this study the prevalence of PDDIs in the CCU's was found to be high, ranging from 92% to 96.9%, which complies with other worldwide studies. The prevalence of PDDIs is comparable to two studies conducted in Abbottabad, Pakistan which reported it to be 91.1% and 77.5% in cardiology patients.[81,281] University of Pittsburg conducted a study in cardiac and cardiothoracic ICU patients, found 87.7% patients having at least a single PDDI.[9] An American study reported the prevalence of PDDIs to be 54.5%.[78] A total of 75% hypertensive patients presented with a PDDIs in another American study.[282] In Switzerland, a study reported 88.8% heart failure patients had PDDIs.[283] It was also reported that 72.5% of ICU patients had PDDIs in a Brazilian hospital,[180] while another Brazilian study reported 87.2% prevalence of PDDIs.[63] Factors like multiple drug therapy, specially the presence of anticoagulant and antiplatelet drugs and complex pathological conditions contribute to the high prevalence of PDDIs in cardiac patients.

In the 3 government hospitals, LRH, KTH and HMC, 76, 95 and 93 interacting drug pairs were identified which contributed to 1204, 1295 and 1253 potential drug-drug interactions, while in the private hospital, 105 interacting drug pairs were identified contributing to 909 PDDIs. One-way ANOVA confirmed this significant difference ($p=0.000$). The difference in prescribing trends contribute to the decreased PDDIs in the private hospital as compared to government hospitals as the use of nitroglycerin tablets was less frequent in the former. The interaction between nitroglycerin and aspirin contributed significantly to the rise in number of PDDIs in the government hospital.

The PDDIs of moderate severity were most prevalent among the hospitals ranging from 52.6% to 54.6%, while according to documentation, most of the PDDIs were of good documentation. Pharmacodynamic type of PDDIs were prevalent in all the hospitals while synergism contributed to the mechanism of majority of PDDIs. A Brazilian study evaluated 1785 prescriptions and recorded a similar trends as seen in this study with the severity of most PDDIs being moderate (78.6%), documentation of most PDDIs was good (29.5%) and most were of pharmacodynamics in nature (43.5%).[175] A Nepalese study reported PDDIs of moderate severity to be the most common (62.5%), while 75.5% of the PDDIs were of good documentation.[64] A study conducted in a CCU of an Iranian hospital reported 75.03% of PDDIs were in Category C, which corresponds to moderate severity.[284] The severity of most of PDDIs was reported to be moderate (61.36% & 60.3%), while pharmacodynamics type of interactions were most prevalent (64.69%) in two Indian studies.[285,286] Record of 1124 patients were evaluated for PDDIs at 24 hours and 120 hours after admission to the hospital. The severity of most interactions was moderate in both the time frames (50.1% and 51.4%), most of the interactions were of good documentation (63.9% and 59.1%) and most of were of pharmacodynamics in nature at 120 hours (45.2%).[181] The findings of the present research complies with those of international researches mentioned above.

A significant association was found between number of interactions and number of prescribed drugs in both private and government setups. A study conducted in United States on hypertensive patients reported a significant association between number of PDDIs and number of prescribed drugs.[179] A Swedish study and an Italian study also displayed significant associations between number of PDDIs and number of prescribed

drugs.[84,59] Similar significant associations between number of PPDIs and number of prescribed drugs were reported in cardiology wards of Pakistan and Brazil.[81,63]

The duration of stay and gender were not significant factors for increase in PDDIs, because the mean duration of stay of patients in this study was low as compared to other studies.[82,81] This difference was due to the fact that there were limited number of beds in the cardiac intensive care units of the hospitals included in this study and high number of patients from the regions of Northwest Pakistan and Afghanistan requiring critical care flock to these hospitals, so patients were shifted to a ward as soon as their condition stabilized slightly making the bed available for new patients, which was a major factor which contributed to the decreased stay duration of the patients in the current study.

The most common interacting drug pairs observed during the study were combinations of antiplatelet, anticoagulant, diuretic, beta blocker, vasodilator and anti-hyperlipidemic drug classes. These drug classes have also been found to be frequently involved in PDDIs in studies conducted at USA,[9,78] Switzerland,[283] Iran[284] and Pakistan.[281,81]

The high prevalence of PDDIs and the morbidity and mortality due to these PDDIs can be minimized by suitably managing frequently occurring and clinically significant PDDIs.

3.3.7 Management guidelines for clinically significant PDDIs

Potential drug-drug interactions having a severity of major or moderate with excellent or good documentation were considered clinically significant and were rated values as 1 and 2. Using this criteria along with the frequency of PDDIs, a list of 13 interacting drug pairs was considered important clinically, because of the associated high risk and occurrence in the cardiac critical care unit.

3.3.7.1 Aspirin + Enoxaparin

The concomitant use of aspirin and enoxaparin results of an increased risk of bleeding. In patients receiving spinal anesthesia or undergoing a spinal puncture, the drug combination may cause epidural or spinal hematomas. However, it is used in myocardial infarction and ischemic conditions of the heart where this PDDI may be considered as beneficial, because of its synergistic action on decreasing platelet function and coagulation. Patients should be monitored closely for any sign and symptom of bleeding and treated accordingly otherwise.[102,100]

3.3.7.2 Ramipril + Spironolactone

Hyperkalemia may be caused due to the concurrent use of ramipril and spironolactone causing severe arrhythmias and death. This is of high risk in geriatric population and patients having renal dysfunction or diabetic disorders. Ramipril and other angiotensin converting enzyme (ACE) inhibitors reduces aldosterone levels which is responsible for the control of sodium and potassium while spironolactone is a potassium sparing diuretic, which also raises serum potassium. Thus the synergistic effect of both these drugs is responsible for the PDDI and the resulting hyperkalemia. Constant monitoring of serum potassium levels is recommended when used concomitantly.[287,189]

3.3.7.3 Clopidogrel + Omeprazole/Esomeprazole

Simultaneous use of clopidogrel with omeprazole or esomeprazole may reduce clopidogrel clinical efficacy and increase the risk of thrombosis. Clopidogrel is converted into its active metabolite by the action of CYP2C19 enzyme, while omeprazole and esomeprazole has an inhibitory effect on this enzyme resulting in the interaction. Omeprazole and esomeprazole is recommended to be replaced with other drugs like pantoprazole or lansoprazole when administering concomitantly with clopidogrel.[137,241,242,138]

3.3.7.4 Digoxin + Spironolactone

Spironolactone inhibits the active tubular secretion of digoxin, thus decreasing the clearance and increasing the exposure of digoxin. The dose of digoxin is recommended to be reduced by 15% to 13% when spironolactone is administered to patients undergoing digoxin therapy. Moreover, spironolactone may also be falsely detected as digoxin in some assays.[245,288]

3.3.7.5 Aspirin + Bisoprolol/Metoprolol/Carvedilol

The antihypertensive effects of beta blockers may be reduced when used with aspirin. The decrease in the production of vasodilator and renal prostaglandins may contribute to its mechanism. Concomitant therapy requires monitoring of patients' blood pressure and dose adjustment of the beta blocker is recommended accordingly.[125]

3.3.7.6 Aspirin + Furosemide

The diuretic and antihypertensive effect of furosemide may be reduced when used concomitantly with aspirin due to the decreased renal prostaglandin production.

Recommendations for concurrent therapy include monitoring of diuretic efficacy and sign and symptoms of renal failure.[122]

3.3.7.7 Aspirin + Spironolactone

Aspirin when used concomitantly with spironolactone may reduce its diuretic efficacy, increase risk of hyperkalemia and nephrotoxicity. The diuretic efficacy is decreased due to the decreased production of renal prostaglandins, while aspirin may also cause hyperkalemia due to hyporeninemic hypoaldosteronism thus having a synergistic effect on the regulation of potassium in blood. Monitoring of parameters like blood pressure, weight, urine output, serum potassium levels and serum creatinine is recommended when these two drugs are administered together.[145]

3.3.7.8 Aspirin + Nitroglycerin

Simultaneous administration of aspirin and nitroglycerin may result in the decreased clearance of nitroglycerin, thus increasing its plasma concentrations. Moreover, depression of the additive platelet function is also reported. Patients having acute myocardial infarction (AMI) may benefit from this interaction. However, monitoring of exaggerated nitroglycerin response, symptomized by headache and syncope, is recommended in non-infarct patients taking analgesic doses of aspirin. Alternate analgesic use is recommended in this situation.[128]

3.3.7.9 Atorvastatin + Clopidogrel

Concurrent use of atorvastatin and clopidogrel may reduce the formation of active metabolite of clopidogrel. Atorvastatin and clopidogrel are both metabolized by CYP3A4 enzymes which results in high on-treatment platelet reactivity. Thus statins which are not metabolized by CYP3A4 like rosuvastatin or pravastatin should be replaced for atorvastatin.[210]

3.3.7.10 Digoxin + Furosemide

Concurrent use of furosemide and digoxin may cause digoxin toxicity, evidenced by nausea, vomiting and arrhythmias. This interaction is a result of potassium and magnesium loss due to furosemide. Serum potassium and even magnesium should be frequently monitored and patients should maintain adequate dietary intake of potassium.[289,213]

3.4 STROKE UNIT (SU)

3.4.1 Northwest General Hospital & Research Center (NWGH & RC)

3.4.1.1 General Patient Characteristics

A total of 240 patients were analyzed of which 145 (60.4%) were males and 95 (39.6%) were females. The mean age of the population was 57.73 years and ranged from 15 to 90 years. Of the total patients, 43.8% were between the ages of 19 to 59 years, 2% were of 18 years and below, while 54.2% patients were of 60 years and above. Mean duration of stay in the critical care unit was 5.62 ± (3.12) days and the mean number of prescribed drugs were 6.03 ± (1.87) as shown in Table 3.121.

The top three leading causes of admission in the SU of NWGH & RC were cerebrovascular accident (CVA), ischemic stroke and brain hemmorhage as shown in Figure 3.13.

Table 3.121 General Patient Characteristics in SU of NWGH & RC

Variables	**Frequency (%)**
Gender	
Male	145 (60.4%)
Female	95 (39.6%)
Age (years)	
Mean ± SD	57.73 (± 17.34)
Median	60
Range	15-90
≤ 18	5 (2%)
19-59	105 (43.8%)
≥ 60	130 (54.2%)
Drugs prescribed per patient	
Mean ± SD	6.03 ± (1.87)
Median	6
Range	2-11
≤ 4	50 (20.8%)
5-6	98 (40.8%)
≥ 7	92 (38.4%)
Stay in ICU (days)	
Mean ± SD	5.62 ± (3.12)
Median	5
Range	1-22
≤ 2	29 (12.1%)
3-5	71 (29.6%)
≥ 6	140 (58.3%)

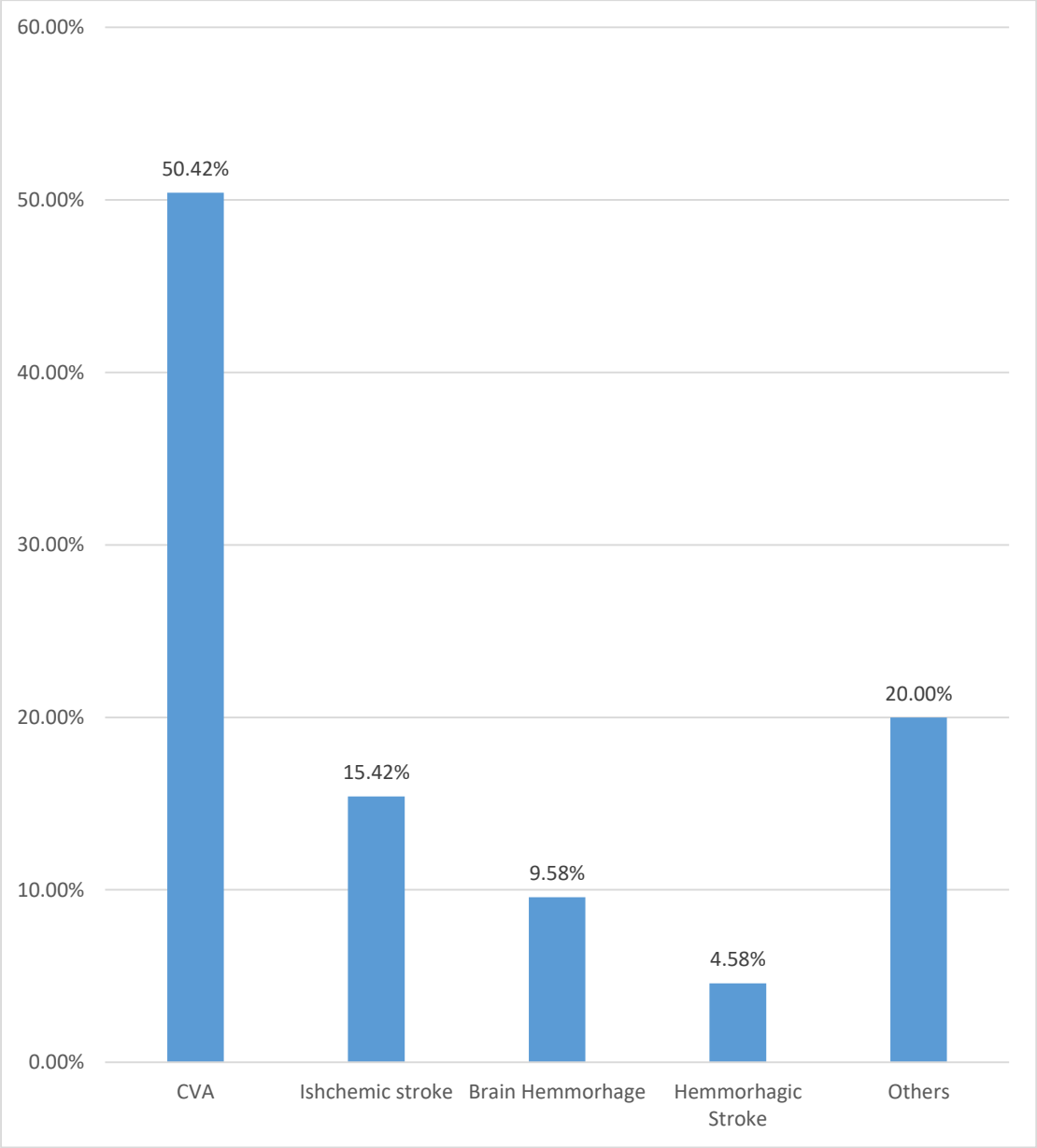

Figure 3.13Causes of admission to SU of NWGH & RC

3.4.1.2 Prevalence of Potential drug-drug interactions

A prevalence of 70.8% PDDIs was reported in the patients of SU of NWGH & RC. Fifty four patients had 2 PDDIs while fifty two patients had 1 PDDI. The prevalence of PDDIs is shown in Table 3.122.

Table 3.122 Prevalence of PDDIs in SU of NWGH & RC

No. of PDDIs	Frequency	Percentage %
1	52	21.7
2	54	22.5
3	26	10.8
4	13	5.4
5	7	2.9
6	9	3.8
7	1	0.1
8	5	2.1
12	1	0.4
19	2	0.8

3.4.1.3 Categories of PDDIs

The PDDIs reported in the SU of NWGH & RC were classified on the basis of severity, documentation, onset and clinical significance. The type and mechanisms of interactions were also identified. A total of 89 interacting drug pairs were identified which caused 474 drug-drug interactions. The severity of 37.6% PDDIs were major, 54% were moderate while 8.4% were of minor severity. Documentation of 29.5% PDDIs were fair, 57% of the PDDIs were of good and 13.5% of the PDDIs were of excellent documentation. On the basis of onset of PDDIs, 53.2% were of unknown onset, 12.2% PDDIs were of rapid and 34.6% were of delayed onset. Pharmacokinetic interactions were present in 40.7% PDDIs, 55.1% PDDIs were of pharmacodynamics type while 4.2% PDDIs were of unknown type. On the basis of mechanisms of PDDIs,

synergism contributed as the mechanism in 32.9% PDDIs, antagonism was involved in 22.1% PDDIs, absorption contributed to 8.9% PDDIs, metabolism contributed for 22.4% PDDIs, elimination contributed in 9.5% PDDIs, while 4.2% PDDIs were of unknown mechanism as shown in Table 3.123.

Table 3.123 Categories of PDDIs in SU of NWGH & RC

Variable	**Frequency (%)**
Severity of PDDIs	
Major	178 (37.6%)
Moderate	256 (54.0%)
Minor	40 (8.4%)
Documentation of PDDIs	
Excellent	64 (13.5%)
Good	270 (57.0%)
Fair	140 (29.5%)
Onset of PDDIs	
Rapid	58 (12.2%)
Delayed	164 (34.6%)
Unkonwn	252 (53.2%)
Type of Interaction	
Pharmacodynamic	261 (55.1%)
Pharmacokinetic	193 (40.7%)
Unknown	20 (4.2%)
Mechanism of Interaction	
Synergism	156 (32.9%)
Antagonism	105 (22.1%)
Absorption	42 (8.9%)
Metabolism	106 (22.4%)
Elimination	45 (9.5%)
Unknown	20 (4.2%)

3.4.1.4 Interacting Drug Pairs

In the SU of NWGH & RC, 89 interacting drug pairs were identified causing 474 drug-drug interactions, of these interacting drug pairs, 7 were involved in 209 (44.1%) interactions of which 3 were major, 3 were moderate and 1 was minor as shown in Table 3.124.

Table 3.124 Interacting drug pairs in SU of NWGH & RC

Interacting Pair	Frequency	Percentage
aspirin-enoxaparin	52	11.0%
dexamethasone-nimodipine	36	7.6%
aspirin-ranitidine	35	7.4%
aspirin-hydrochlorothiazide	27	5.7%
aspirin-ramipril	22	4.6%
aspirin-clopidogrel	19	4.0%
aspirin-dexamethasone	18	3.8%
aspirin-irbesartan	17	3.6%
aspirin-furosemide	13	2.7%
aspirin-valsartan	13	2.7%
amlodipine-dexamethasone	13	2.7%
aspirin-amlodipine	11	2.3%
clopidogrel-enoxaparin	11	2.3%
aspirin-carvedilol	10	2.1%
enoxaparin-warfarin	7	1.5%
omeprazole-phenytoin	7	1.5%
nimodipine-valproate	7	1.5%
ramipril-spironolactone	7	1.5%
aspirin-spironolactone	7	1.5%
ramipril-furosemide	6	1.3%
dexamethasone-phenytoin	5	1.1%

amlodipine-aspirin	5	1.1%
dexamethasone-moxifloxacin	5	1.1%
aspirin-nitroglycerin	4	0.8%
acyclovir-phenytoin	4	0.8%
aspirin-heparin	4	0.8%
aspirin-warfarin	3	0.6%
amlodipine-clopidogrel	3	0.6%
aspirin-bisoprolol	3	0.6%
atorvastatin-diltiazem	3	0.6%
carbamazepine-dexamethasone	3	0.6%
amlodipine-bisoprolol	3	0.6%
clopidogrel-rabeprazole	3	0.6%
rosuvastatin-warfarin	3	0.6%
atorvastatin-digoxin	3	0.6%
carbamazepine-hydrochlorothiazide	3	0.6%
esomeprazole-warfarin	3	0.6%
aspirin-indapamide	3	0.6%
hydrocortisone-moxifloxacin	2	0.4%
albuterol-bisoprolol	2	0.4%
co-amoxiclav-warfarin	2	0.4%
clarithromycin-atorvastatin	2	0.4%
rifampin-isoniazid	2	0.4%
dexamethasone-rifampin	2	0.4%
pyrazinamide-rifampin	2	0.4%
atorvastatin-clopidogrel	2	0.4%
aspirin-lisinopril	2	0.4%
spironolactone-warfarin	2	0.4%
amlodipine-carvedilol	2	0.4%
lisinopril-furosemide	2	0.4%
amlodipine-atenolol	2	0.4%
amlodipine-nebivolol	2	0.4%

metronidazole-phenytoin	2	0.4%
nimodipine-phenytoin	2	0.4%
aspirin-nebivolol	2	0.4%
aspirin-diltiazem	2	0.4%
lisinopril-spironolactone	2	0.4%
bisoprolol-nimodipine	2	0.4%
clopidogrel-warfarin	2	0.4%
metronidazole-warfarin	2	0.4%
clarithromycin-phenytoin	1	0.2%
ketorolac-phenytoin	1	0.2%
clarithromycin-moxifloxacin	1	0.2%
aspirin-perindopril	1	0.2%
irbesartan-potassium	1	0.2%
clopidogrel-omeprazole	1	0.2%
aspirin-fondaparinux	1	0.2%
meropenem-valproate	1	0.2%
aspirin-losartan	1	0.2%
metronidazole-moxifloxacin	1	0.2%
levofloxacin-metronidazole	1	0.2%
ceftriaxone-warfarin	1	0.2%
aspirin-nimodipine	1	0.2%
albuterol-digoxin	1	0.2%
phenytoin-ranitidine	1	0.2%
omeprazole-warfarin	1	0.2%
amlodipine-phenytoin	1	0.2%
enoxaparin-heparin	1	0.2%
clopidogrel-diltiazem	1	0.2%
losartan-ramipril	1	0.2%
aspirin-levofloxacin	1	0.2%
ranitidine-warfarin	1	0.2%
phenytoin-quinine	1	0.2%

hydrocortisone-phenytoin	1	0.2%
carvedilol-digoxin	1	0.2%
aspirin-hydrocortisone	1	0.2%
diltiazem-ranitidine	1	0.2%
hydrocortisone-levofloxacin	1	0.2%
digoxin-diltiazem	1	0.2%

3.4.1.5 Clinically significant PDDIs in SU of NWGH & RC

Analysis of the drug interacting pairs for clinical significance yielded 58 pairs having a clinical significance of 1 and 2. These pairs contributed to 58.2% of the total PDDIs (276 of 474), 17 of which were of clinical significance 1 while 41 were of clinical significance 2. The clinically significant drug interacting pairs along with their potential outcomes are shown in Table 3.125.

Table 3.125 Clinically important interacting pairs and their potential outcomes in SU of NWGH & RC

Interacting drug pairs	Clinical significance	Frequency	Potential Outcome	References
Aspirin-enoxaparin	1	52	Increased risk of bleeding.	105,106
Clopidogrel-omeprazole	1	1	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.	136,137
Ramipril-spironolactone	1	7	May result in hyperkalemia.	189,190
Amlodipine-clopidogrel	1	3	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Aspirin-warfarin	1	1	Increased risk of bleeding.	22,23
Clopidogrel-diltiazem	1	1	Decreased antiplatelet effect and increased risk of thrombotic events.	207,208
Losartan-ramipril	1	1	Increased risk of adverse events (i.e., hypotension, syncope, hyperkalemia, changes in renal function, acute renal failure).	262
Clopidogrel-rabeprazole	1	7	May result in increased risk for thrombosis.	139,241
Co-amoxiclave-warfarin	1	1	Increased risk of bleeding.	134
Lisinopril-spironolactone	1	2	May result in hyperkalemia.	189,190
Atorvastatin-diltiazem	1	3	Increased risk of rhabdomyolysis.	256,257

Atorvastatin-clarithromycin	1	2	Increased atorvastatin exposure and an increased risk of myopathy or rhabdomyolysis.	130,131
Meropenem-valproate	1	1	Decreased valproic acid plasma concentrations and loss of anticonvulsant effect.	96,97,98,99
Isoniazid-rifampin	1	2	Hepatotoxicity	202
Pyrazinamide-rifampin	1	2	Severe hepatic injury.	203
Metronidazole-warfarin	1	2	Increased risk of bleeding.	290
Nimodipine-phenytoin	1	2	Reduced nimodipine plasma concentrations and reduced nimodipine efficacy.	107
Aspirin-dexamethasone	2	18	Increased risk of gastrointestinal ulceration and subtherapeutic aspirin serum concentrations.	142,115
Aspirin-nebivolol	2	2	May result in decreased antihypertensive effect.	165
Aspirin-nitroglycerin	2	4	May result in an increase in nitroglycerin concentrations and additive platelet function depression.	124,125
Furosemide-ramipril	2	6	May result in postural hypotension (first dose).	151
Furosemide-lisinopril	2	2	May result in postural hypotension (first doe).	151
Aspirin-furosemide	2	13	May result in decreased diuretic and antihypertensive efficacy.	121,122
Aspirin-spironolactone	2	7	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.	123

Aspirin-carvedilol	2	10	May result in decreased antihypertensive effect.	[124,125]
Aspirin-bisoprolol	2	3	May result in decreased antihypertensive effect.	[124,125]
Aspirin-losartan	2	1	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-valsartan	2	12	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-irbesartan	2	17	May result in decreased antihypertensive effects and an increased risk of renal impairment.	[127]
Aspirin-amlodipine	2	16	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[141]
Aspirin-hydrochlorothiazide	2	17	Decreased diuretic and antihypertensive efficacy.	[145]
Amlodipine-bisoprolol	2	2	May result in hypotension and/or bradycardia.	[152,153]
Amlodipine-carvedilol	2	2	May result in hypotension and/or bradycardia.	[152,153]
Amlodipine-atenolol	2	2	May result in hypotension and/or bradycardia.	[152,153]
Amlodipine-nebivolol	2	2	May result in hypotension and/or bradycardia.	[152,153]
Aspirin-diltiazem	2	2	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[112]
Aspirin-lisinopril	2	2	May result in decreased lisinopril effectiveness.	[230]
Atorvastatin-clopidogrel	2	2	Decreased formation of clopidogrel active metabolite	[210]
Ceftriaxone-warfarin	2	1	Increased risk of bleeding.	[158]

Hydrocortisone-moxifloxacin	2	2	Increased risk of tendon rupture.	[165]
Hydrocortisone-levofloxacin	2	1	Increased risk of tendon rupture.	[165]
Omeprazole-warfarin	2	1	May result in elevations of INR serum values and potentiation of anticoagulant effects.	[157]
Esomeprazole-warfarin	2	3	May result in elevations of INR serum values and potentiation of anticoagulant effects.	[157]
Dexamethasone-phenytoin	2	5	Decreased dexamethasone effectiveness.	[107]
Aspirin-nimodipine	2	1	Increased risk of gastrointestinal hemorrhage and/or antagonism of hypotensive effect.	[143,144]
Clarithromycin-phenytoin	2	1	Decreased clarithromycin plasma concentrations.	[126,156]
Acyclovir-phenytoin	2	4	Decreased phenytoin plasma concentrations and potential increased seizure activity.	[195]
Dexamethasone-rifampin	2	2	May result in decreased dexamethasone effectiveness	[120]
Atorvastatin-digoxin	2	3	Increased plasma concentrations of digoxin.	[250]
Carvedilol-digoxin	2	1	Increased risk of bradycardia and possible digitalis glycoside toxicity.	[251]
Dexamethasone-moxifloxacin	2	5	Increased risk of tendon rupture.	[165]
Aspirin-indapamide	2	3	Decreased diuretic and antihypertensive efficacy.	[145]

Bisoprolol-nimodipine	2	2	May result in hypotension and/or bradycardia.	[152]
Carbamazepine-hydrochlorothiazide	2	3	May result in hyponatremia.	[291]
Digoxin-diltiazem	2	1	Increased serum digoxin concentrations and toxicity (nausea, vomiting, arrhythmias).	[292]
Phenytoin-quinine	2	1	Decreased quinine plasma concentrations and efficacy.	[201]
Ranitidine-warfarin	2	1	Increased risk of bleeding.	[293]
Rosuvastatin-warfarin	2	3	May result in increase in international normalized ratio (INR) and increased risk of bleeding.	[248]

3.4.1.6 Association of PDDIs with other parameters in SU of NWGH & RC

The association of prescribed drugs, duration of stay and gender with PDDIs was determined using multiple logistic regression to calculate the odds ratio (OR) with 95% confidence interval (CI) and significance (p)

There was a significant association between the presence of PDDIs with the patients prescribed 6 or more drugs (OR = 6.056; 95%CI = 3.247-11.293; p = 0.000). An insignificant association was found between the presence of PDDIs and duration of stay of 5 or more days (OR = 1.304; 95%CI = 0.702-2.422; p = 0.401), and with gender (OR = 0.816; 95%CI = 0.438-1.519; p = 0.521). The results are shown in Table 3.126.

Table 3.126 logistic regression analysis in SU of NWGH & RC

Variable	**Patients n**		**OR (95%CI)**	**p-value**
	Interactions present (n=170)	**Interactions absent (n=70)**		
Prescribed drugs				
< 6	48	50		
≥ 6	122	20	6.056 (3.247-11.293)	0.000
Duration of stay				
< 5	65	35		
≥ 5	105	35	1.304 (0.702-2.422)	0.401
Gender				
Male	106	39		
Female	64	31	0.816 (438-1.519)	0.521

3.4.1.7 Drugs used

A total of 105 drugs were prescribed in the SU of NWGH & RC appearing 1444 times in all the medication charts as shown in Table 3.127.

Table 3.127 Frequencies of commonly used drugs in SU of NWGH & RC

Drug Name	Dosage Form	Frequency
Ceftriaxone	Intravenous	167
Aspirin	Tablets	113
Rosuvastatin	Tablets	108
Omeprazole	Intravenous	82
Enoxaparin	Subcutaneous	65
Dexamethasone	Intravenous	64
Esomeprazole	Intravenous	63
Nimodipine	Tablets	61
Albuterol	Nebules	47
Amlodipine	Tablets	43
Atorvastatin	Tablets	42
Ranitidine	Intravenous	38
Irbesartan+hydrochlorothiazide	Tablets	35
Ramipril	Tablets	32
Metronidazole	Intravenous	31
Co-amoxiclav	Intravenous	30
Ipratropium	Nebules	29
Perindopril	Tablets	22
Dimenhydrinate	Intravenous	21
Metoclopramide	Intravenous	19
Lactulose	Syrup	18
Tramadol	Intravenous	15
Valsartan+hydrochlorothiazide	Tablets	14
Moxifloxacin	Intravenous	13
Clopidogrel+aspirin	Tablets	11

Phenytoin	Intravenous	11
Acyclovir	Intravenous	11
Warfarin	Tablets	11
Carvedilol	Tablets	11
Piperacillin+tazobactam	Intravenous	10
Beclomethasone	Nebules	10
Clopidogrel	Tablets	9
Valproate sodium	Intravenous	9
Levetiracetam	Tablets	9
Bisoprolol	Tablets	7
Furosemide+spironolactone	Tablets	7
Levetiracetam	Intravenous	7
Furosemide	Intravenous	6
Ranitidine	Tablets	6
Meropenem	Intravenous	6
Vancomycin	Intravenous	6
Hydrocortisone	Intravenous	6
Tramadol	Tablets	6
Heparin	Subcutaneous	5
Digoxin	Tablets	4
Amlodipine+valsartan	Tablets	4
Nitroglycerin	Tablets	4
Rabeprazole	Tablets	4
Levetiracetam	Syrup	4
Diltiazem	Tablets	3
Clarithromycin	Intravenous	3
Enalapril+hydrochlorothiazide	Tablets	3
Carbamazepine	Tablets	3
Atenolol	Tablets	3
Colistimethate	Intravenous	3
Ceftazidime	Intravenous	3
Baclofen	Tablets	3
Idapamide	Tablets	3

Cefoperazone+sulbactam	Intravenous	2
Nebivolol	Tablets	2
Tranexamic acid	Intravenous	2
Piracetam	Intravenous	2
Streptomycin	Intramuscular	2
Levofloxacin	Intravenous	2
Lisinopril	Tablets	2
Calcium gluconate	Intravenous	2
Vitamin K	Intravenous	2
Sodium picosulfate	Syrup	2
Pyridoxine	Tablets	2
Isoniazid	Tablets	2
Pyrazinamide	Tablets	2
Rifampin	Tablets	2
Imipenem+cilastatin	Intravenous	1
Valsartan	Tablets	1
Fondaparinux	Subcutaneous	1
Losartan	Tablets	1
Linezolid	Intravenous	1
Ketorolac	Intravenous	1
Nifedipine	Tablets	1
Cefuroxime	Intravenous	1
Irbesartan	Intravenous	1
Rifaximin	Tablets	1
Haloperidol	Tablets	1
Quinine	Intravenous	1
Artemether+lumefantrine	Tablets	1
Nalbuphine	Intravenous	1
Folic acid	Tablets	1
Esomeprazole	Tablets	1
Methyldopa	Tablets	1
Pantoprazole	Intravenous	1
Calcitriol	Intravenous	1

Domperidone	Syrup	1
Bromocriptine	Tablets	1
Clonazepam	Tablets	1
Potassium chloride	Tablets	1
Azithromycin	Tablets	1
Pregabalin	Tablets	1
Piracetam	Tablets	1
Paracetamol	Tablets	1
Codergocrine	Tablets	1
Procyclidine	Tablets	1
Lamotrigine	Tablets	1
Nortriptyline	Tablets	1
Propofol	Intravenous	1
Risperidone	Tablets	1

3.4.1.8 Indications

Secondary infection was the most prevalent indication in the SU of NWGH & RC (264 cases of 1444) followed by stress ulcer (193 cases), hypertension (171 cases), hyperlipidemia (150 cases), CVA (110 cases), asthma (84 cases) and subarachnoid hemorrhage (61 cases), while the rest of the cases were contributed by other indications.

3.4.1.9 Drug class

A total of 34 drug classes were used in the SU of NWGH & RC with antibacterial being the most prevalent drug class as shown in Table 3.128.

Table 3.128 Frequencies of Drug classes used in SU of NWGH & RC

Drug Class	Frequency
Antibacterial	283
Proton Pump Inhibitors	151
HMG Co-A reductase inhibitor	150
Antiplatelet	119
Calcium channel blocker	108
Anticoagulant	99
Corticosteroid	80
Bronchodilator	76
ACE inhibitors	59
ARBs	53
Anticonvulsant	45
H2 receptor antagonist	44
Antiemetic	41
Analgesic	26
Beta blocker	23
Laxative	19
Diuretic	16
Antiviral	11
Nutriceutical	8
Antitubercular	6
Cardiac glycoside	4
Nitrates	4
Nootropic agent	3
Antimalarial	2
Antipsychotic	2
Antiparkinsonian	2
Neuropathic pain agent	2
Hemostatic	1
Antianemic	1
Alpha adrenergic agonist	1

Liver protectant	1
Ergot alkaloid	1
Sedative	1
Antiplasminic agent	1

3.4.1.10 Dosing errors in SU of NWGH & RC

Out of the total 1444 cases, 142 (9.8%) had subtherapeutic doses while 24 (1.7%) had overdoses as shown in Table 3.129 and Table 3.130 respectively.

Table 3.129 Frequencies of drugs prescribed with subtherapeutic dose

Drug Name	Dosage Form	Frequency
Nimodipine	Tablets	38
Ranitidine	Intravenous	30
Co-amoxiclav	Intravenous	19
Piperacillin + tazobactam	Intravenous	10
Metoclopramide	Intravenous	7
Dexamethasone	Intravenous	5
Ranitidine	Tablets	4
Nitroglycerin	Tablets	4
Carvedilol	Tablets	4
Carbamazepine	Tablets	3
Enoxaparin	Subcutaneous	3
Meropenem	Intravenous	2
Phenytoin	Intravenous	2
Clarithromycin	Intravenous	2
Clonazepam	Tablets	1
Azithromycin	Tablets	1
Cefuroxime	Intravenous	1
Ceftriaxone	Intravenous	1
Heparin	Subcutaneous	1
Piracetam	Tablets	1
Nifedipine	Tablets	1
Dilitazem	Tablets	1
Artemether + lumefantrine	Tablets	1

Table 3.130 Frequencies of drugs prescribed in overdoses

Drug Name	Dosage Form	Frequency
Aspirin	Tablets	5
Amlodipine	Tablets	3
Dexamethasone	Intravenous	3
Calcium gluconate	Intravenous	2
Ranitidine	Tablets	2
Valsartan+hydrochlorothiazide	Tablets	2
Ipratropium	Nebules	2
Beclomethasone	Nebules	1
Bisoprolol	Tablets	1
Tranexamic acid	Intravenous	1
Enoxaparin	Subcutaneous	1
Albuterol	Nebules	1

3.4.2 DISCUSSION

Stroke is one of the devastating and most common neurological disorder in the world responsible for morbidity and mortality.[294,295] In USA it is estimated to be the third most common cause of mortality.[296] Several studies have demonstrated stroke rising rapidly in Pakistan.[297,298,299] However, studies are lacking to identify the prevalence of PDDIs in specialized stroke units and stroke patients.

A predominant male population was encountered in this study (60.4%), male predominance in stroke was presented in a study conducted in Pakistan and in a Dutch study as well.[295,300] A systematic review conducted from different articles confirmed that stroke is predominant in male gender but the reason behind this gender specificity cannot be confirmed, and male gender is considered a strong risk factor.[301]

The prevalence of PDDIs was 70.8% while most of the PDDIs were of moderate severity (54%) and of good documentation (57%). The onset of 53.2% interactions was unknown while most of the interactions were of pharmacodynamics type (55.1%) with synergism (32.9%) being the dominant mechanism.

High prevalence rates of PDDIs in other specialized critical care units have been reported.[78,9,180] Brazilian studies reported PDDIs of moderate severity to be the most common.[302,175] An Indian study also reported PDDIs of moderate severity and pharmacodynamic nature to be the most common.[286] Although these were not studies relating to stroke patients but due to the close similarity of drug classes used and PDDIs in these studies, were chosen as specialized stroke studies are lacking.

A significant association was found between number of interactions and number of prescribed drugs in this study. This significant association is consistent with many international studies. A study conducted in United States on hypertensive patients reported a significant association between number of PDDIs and number of prescribed drugs.[179] An Ethiopian study revealed a significant association between these two factors when patient received three or more drugs.[177] An Indian study reported a significant positive association between these two factors.[178] While various Pakistani, Iranian, Brazilian, Italian, Swedish and American studies also reported a significant association between number of interactions and number of prescribed drugs.[81,84,63,59,179]

The most common drugs involved in PDDIs included antiplatelets, anticoagulants, antihypertensive, diuretics and corticosteroids. Managing these clinically significant PDDIs can greatly reduce the occurrence of adverse events associated with them.

3.4.3 Management guidelines for clinically significant PDDIs

Potential drug-drug interactions having a severity of major or moderate with excellent or good documentation were considered clinically significant and were rated values as 1 and 2. Using this criteria along with the frequency of PDDIs, a list of 10 interacting drug pairs was considered important clinically, because of the associated high risk and occurrence in the stroke unit.

3.4.3.1 Aspirin + Enoxaparin

The concomitant use of aspirin and enoxaparin results of an increased risk of bleeding. In patients receiving spinal anesthesia or undergoing a spinal puncture, the drug combination may cause epidural or spinal hematomas. However, it is used in myocardial infarction and ischemic conditions of the heart where this PDDI may be considered as beneficial, because of its synergistic action on decreasing platelet function and coagulation. Patients should be monitored closely for any sign and symptom of bleeding and treated accordingly otherwise.[102,100]

3.4.3.2 Ramipril + Spironolactone

Hyperkalemia may be caused due to the concurrent use of ramipril and spironolactone causing severe arrhythmias and death. This is of high risk in geriatric population and patients having renal dysfunction or diabetic disorders. Ramipril and other angiotensin converting enzyme (ACE) inhibitors reduces aldosterone levels which is responsible for the control of sodium and potassium while spironolactone is a potassium sparing diuretic, which also raises serum potassium. Thus the synergistic effect of both these drugs is responsible for the PDDI and the resulting hyperkalemia. Constant monitoring of serum potassium levels is recommended when used concomitantly.[287,189]

3.4.3.3 Clopidogrel + Rabeprazole

Simultaneous use of clopidogrel with rabeprazole may reduce clopidogrel clinical efficacy and increase the risk of thrombosis. Clopidogrel is converted into its active metabolite by the action of CYP2C19 enzyme, while rabeprazole has an inhibitory effect on this enzyme resulting in the interaction. rabeprazole is recommended to be replaced with other drugs like pantoprazole or lansoprazole when administering concomitantly with clopidogrel.[137,241,242,138]

3.4.3.4 Aspirin + Dexamethasone

The concurrent use of aspirin with dexamethasone may increase the risk of gastrointestinal bleeding and reduced plasma concentrations of aspirin. The synergistic action of both these drugs is the responsible mechanism for this adverse reaction. Moreover, dexamethasone increases the clearance of aspirin. Monitoring signs and symptoms of gastrointestinal bleeding along with the effectiveness of aspirin is recommended.[114]

3.4.3.5 Aspirin + Furosemide

The diuretic and antihypertensive effect of furosemide may be reduced when used concomitantly with aspirin due to the decreased renal prostaglandin production. Recommendations for concurrent therapy include monitoring of diuretic efficacy and sign and symptoms of renal failure.[122]

3.4.3.6 Aspirin + Spironolactone

Aspirin when used concomitantly with spironolactone may reduce its diuretic efficacy, increase risk of hyperkalemia and nephrotoxicity. The diuretic efficacy is decreased due to the decreased production of renal prostaglandins, while aspirin may also cause hyperkalemia due to hyporeninemic hypoaldosteronism thus having a synergistic effect on the regulation of potassium in blood. Monitoring of parameters like blood pressure, weight, urine output, serum potassium levels and serum creatinine is recommended when these two drugs are administered together.[145]

3.4.3.7 Aspirin + Carvedilol

The antihypertensive effects of beta blockers may be reduced when used with aspirin. The decrease in the production of vasodilator and renal prostaglandins may contribute to its mechanism. Concomitant therapy requires monitoring of patients' blood pressure and dose adjustment of the beta blocker is recommended accordingly.[125]

3.4.3.8 Aspirin + Amlodipine

Concomitant use of aspirin and amlodipine may result in increased risk of gastrointestinal (GI) bleeding and decreased hypotensive effect of amlodipine. Mechanisms involve decrease in the production of renal prostaglandins, while GI bleeding is due to the synergistic adverse effect. Monitoring of signs and symptoms of GI bleeding and clinical effect is recommended.[154,183]

3.4.3.9 Aspirin + Hydrochlorothiazide

Diuretic and antihypertensive effect of hydrochlorothiazide may be reduced when used concurrently with aspirin. The decrease in renal prostaglandin production is responsible for this interaction. Patient should be monitored for the diuretic effect and sign and symptoms of renal failure like urine output and edema.[145]

3.4.3.10 Furosemide + Ramipril

Postural hypotension may be caused by the concurrent use of furosemide and ramipril, due to the synergistic vasodilator effect. Furosemide should be discontinued for 2 or 3 days before initiating ramipril therapy. If concurrent administration is unavoidable, ramipril therapy should be initiated by administering a very low dose in the evening and monitoring signs for severe hypotension for four hours. Regular monitoring of blood pressure, fluid status and weight of the patient is required for up to 2 weeks after the dose is adjusted.[303]

Conclusion

4 Conclusion

The present study shows a high prevalence of potential drug-drug interactions (PDDIs) in the critical care units of the four tertiary care hospitals. This is an alarming situation as minor adverse effects resulting from PDDIs can drastically deteriorate the already critical nature of the patients admitted to these units. Moreover, it was also found that almost 50% of these PDDIs were clinically significant but only attributed to a limited number of interacting pairs. Another factor for difference in the prevalence of PDDIs among hospitals was the use of drugs having higher risk of drug interactions when therapeutic alternatives with lower risk were present. But due to the prescribing trends of physicians, these alternatives were not used resulting in higher PDDIs. When compared to recommended doses, deviations were found in almost 7.5% of patients. So avoiding clinically significant PDDIs, proper education regarding the PDDIs, specially the clinically significant ones must be provided to the physicians to avoid drastic adverse effects of the interacting drugs. The management guidelines of the clinically significant PDDIs have been provided in this thesis as an initiative. Further studies of this nature are needed to be performed to elucidate problems in our health care system and to improve the health of the society.

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