NEAR EAST UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CLINICAL PHARMACY

ASSESSMENT OF POTENTIAL DRUG-DRUG INTERACTIONS IN PATIENTS WHO UNDERWENT CARDIAC SURGERY AT A SURGICAL CARDIAC CENTER IN ERBIL, IRAQ

M.Sc. THESIS

SIMA SIYAMAND HUSSEIN

Northern Cyprus, Nicosia
February , 2022

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Northern Cyprus, Nicosia
February , 2022

Approval

We certify that we have read the thesis submitted by Sima Hussein titled **"Assessment of Potential Drug-drug Interactions in Patients Who Underwent Cardiac Surgery at a Surgical Cardiac Center in Erbil, Iraq"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of since in Clinical Pharmacy.

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Declaration

I, Sima Hussein, declare that the thesis hereby submitted to the Near East University for the degree of Master of Clinical Pharmacy, in the School of Pharmacy, has not previously been submitted to this or any other university; that it is my work in design and execution; and that all material contained herein has been duly acknowledged.

Sima Hussein

29/03/2022

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Sima Hussein

Abstract

Assessment of Potential Clinically Significant Drug-drug Interactions in Patients Underwent Cardiac Surgery at a Surgical Cardiac Center in Erbil, Iraq.

Sima Hussein

MA, Department of Clinical Pharmacy

February ,2022.

Introduction: Drug-drug interactions (DDIs) are a major problem in hospitals that result in adverse drug reactions. Patients in the surgical department are likely to have possible DDIs, which can result in morbidity and mortality.

Aim: The aim of the study was to assess the prevalence of drug-drug interactions, to investigate factors associated with drug-drug interactions, and to compare DDI programs Checkers for evaluating the accuracy of patients admitted for Cardiothoracic Surgery (CTS) in surgical specialty hospital cardiac center in Erbil/Iraq while they were hospitalized.

Method: A Retrospective study was carried out and the data was collected from the 300 patients` archives file of inpatients who underwent cardiac surgery between January 2020 and February 2021. Stockley's Drug Interactions, Micromedex, and Lexicomp DI checkers were used to analyze and classify potential drug interactions and their accuracy was assessed in detecting DDIs Mann-Whitney U test and Kruskal-Wallis test was used for the comparisons between variables. A p-value of < 0.05 was considered statistically significant.

Result: The prevalence of pDDIs was 97.3%. Pharmacodynamics mechanism of interaction was most common 65.4% and the majority of them were major in severity (59.3%). there was significant association of pDDIs occurrence with age ($p< 0.05$), duration of stay in hospital ($p< 0.05$), polypharmacy ($p< 0.05$), comorbidities ($p<0.05$).

Conclusion: Drug-drug interactions were common in Cardiothoracic Surgery (CTS) patients. The prevalence of DDIs in this population was found to be high. Even though Micromedex detects more major interactions than Lexicomp. Polypharmacy, age, duration of stay in the hospital, and comorbidities had significant associations with the number of DDIs. ***Key Words:*** Drug-drug interaction, Hospitalized cardiac surgery, Risk Factors, Surgical Specialty Hospital -Cardiac Center, Erbil/Iraq.

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List of Abbreviations

A.A.A:	Abdominal Aortic Aneurysm
ADR:	Adverse drug reaction
ASD:	Atrial Septal Defect
AVR:	Aortic valve Replacement
CABG:	Coronary Artery Bypass Graft
CCU:	Critical Care Unit
CP:	Clinical Pharmacy
CTS	Cardiothoracic Surgery
CVD:	Cardiovascular Disease
DDI:	Drug-Drug interaction
DRP:	Drug related problem
DVT:	Deep vein thrombosis
FDA:	Food and Drug Administration
HT:	Hypertension
MVR:	Mitral valve replacement
NEU:	Near East University
NSAID:	Non-steroidal anti-inflammatory drugs
OMT:	Osteopathic Manipulative Treatment
OTC:	Over the counter drugs
PC:	Pharmaceutical Care
PCI:	Percutaneous coronary intervention
PD:	Pharmacodynamics
PD:	Pharmacodynamics
PDDI:	Potential drug-drug interaction
PK:	Pharmacokinetics
PK:	Pharmacokinetics
SD:	Standard Deviation
TR:	Tricuspid regurgitation
WHO:	World Health Organization

CHAPTER I

Introduction

1.1 Background and Rationale for the Study:

Cardiovascular diseases (CVD) continue to be the major cause of death globally (WHO, 2015). In 2012, an estimated 17.5 million people died from cardiovascular disease, accounting for 31% of all deaths worldwide, with 7.4 million deaths from coronary heart disease with 6.7 million dying from stroke (WHO, with15). Out of the 16 million deaths of persons under the age of 70 caused by non-communicable illnesses, 82% occur in poor and middle-income countries, with Cardiovascular Disease (CVD)s accounting for 37% (Chen et al., 2017).

1.2 Drug-related problems:

Therapeutic effects are achieved when the appropriate medicine, in the appropriate quantity and quality, is administered to the right patient at the appropriate time. Inappropriate drug usage, on the other hand, might have negative consequences.(Fijn et al., 2002) . Drug-Related Problems (DRPs) are seen as a challenge to clinicians since they might alter patient outcomes, resulting in morbidity or mortality and increasing healthcare costs. Clinical pharmacy practices include improving drug use through evidence-based guidelines, as well as recognizing and addressing DRPs (Parthasarathi et al., 2003). When incidences of aplastic anemia were recorded following the usage of chloramphenicol, DRPs became a topic of discussion (RICH et al., 1950). and birth abnormalities as a result of thalidomide therapy in 1960 (Mellin & Katzenstein, 1962).

Drug-Related Problems are defined as any occurrences or circumstances that actually or negatively affect the anticipated treatment effects Mellin and Katzenstein (1962). A real problem causes clinical signs (such as a harmful medication reaction or drug-related rash) or therapeutic failure due to inappropriate dosage. A possible problem is not obvious, and if left unresolved, it may result in drug-related harm to the patient (Viktil & Blix, 2008).

Medication errors (MEs), adverse drug events (ADEs), and adverse drug reactions Adverse Drug Reaction (ADR) are all examples of DRPs (ADRs) (Dean et al., 1995). DRP is further subdivided into toxicities of both intrinsically and extrinsically. Internal toxicity, or Adverse Drug Reaction (ADR)s, refers to the interaction of the pharmaceutical chemical and/or pharmacological properties of the medicines with the human bio-system. (Edwards & Aronson, 2000) Extrinsic toxicity, often known as MEs, refers to issues produced by inappropriate drug usage, whether by a healthcare practitioner or a patient (Gonzales, 2010).

The following terms are described in further detail;

Drug-related problems (DRPs): All actual or possible problems that a patient has as a result of pharmacological treatment that interfere with the patient's ability to achieve the targeted treatment outcome (Imfeld-Isenegger et al., 2017).

Medication error (ME): When a medicine is still being used by healthcare practitioners or patients, an avoidable occurrence may occur, resulting in irrational use or patient risk (Horvat & Kos, 2016)Adverse drug event (ADE): An unanticipated occurrence that occurs during medical therapy and is not usually linked to the therapy (Horvat & Kos, 2016).

Adverse drug reaction (ADR): An unanticipated and adverse reaction to a medicine.And it happens at doses that are commonly employed in humans for illness prevention, diagnosis, or treatment, as well as the change of physiological functioning (Horvat & Kos, 2016).

1.3 Drug-Related Problem Risk Factors:

It is critical to understand the risk factors for DRPs in order to design preventative methods to mitigate their recurrence. Receiving a high number of medications, being female, taking the drug with narrow therapeutic index, renal elimination of pharmaceuticals, older than sixty-five years old, and the use of medicines for diuretic effect and medicines for prevention of coagulation and thrombosis are all important factors to develop adverse drug reactions (Krähenbühl-Melcher, 2005).

In addition, Leendertse et al. analyze more specific risk factors, such as 4 or more comorbidities, a dependent living situation, reduced cognition, abnormal renal function, and non-adherence to the drug regimen (Leendertse et al., 2008).

1.4 Problems related to drugs in hospitalized patients drug-related issues:

They are common in hospital admissions and therefore can increase suffering, mortality, and costs. (Kongkaew et al., 2008) Furthermore, past research has shown that DRPs are the leading cause of hospitalization (Blix et al., 2004). According to a study done by Urbina et al. (2015) in hospitalized the cardiology ward of a teaching hospital in 2009. Demonstrated that in all, 448 DRPs were detected, drug-drug or drug-food interactions, were mainly involving ADRs were connected to 5.3 percent of hospital admissions in a comprehensive review of 25 prospective observational studies that used the WHO criteria of ADR. Patients above the age of 65 had the highest rates while using several medications for long-term illnesses. (Kongkaew et al., 2008).

Some other review of publications period between 1990 through 2005 on drug-related issues in hospitals discovered that MEs affect roughly 5% of hospitalized patients, while ADEs affect about 6%. (Krähenbühl-Melcher, 2005). Furthermore, Van den Bemt and colleagues discovered that Medication errors (1.7–59%) and Adverse drug reactions (1.9–37.3%) are more common in hospital admissions compared ADEs (0.7 to 6.5 percent). (van den Bemt et al., 2000). Medication-related hospitalizations can be avoided. According to a prospective research on the frequency of unnecessary drug-related hospital admissions in the Netherlands of 12793 unplanned hospitalizations 5.6 % have been drug-related, and 46.5 percent of these admissions were most likely avoidable (Leendertse et al., 2008).

Moreover, even significant Adverse events seem to be more likely to be avoidable. A 6-month prospective study found 247 Adverse drug events and 194 potential Adverse drug events. 70 (28%) of the 247 Adverse drug events were avoidable, and 83 percent of the potential Adverse drug events were identified before the medications were provided (Bates et al., 1995).

1.5 Aim of The study:

Our study aimed to assess the prevalence of drug-drug interactions, to investigate factors associated with drug-drug interactions and to compare DDI programs Checkers for evaluating the accuracy of patients admitted for CTS in surgical specialty hospital cardiac center in Erbil/Iraq while they were hospitalized.

The objectives of the study were as follows:

1. To assess Demographic Data, Clinical Information, and Clinical Drug Information Variables.
2. To find out the top ten of most Repeated Drug-drug Interaction Pairs of each type of Drug-drug Interaction Pairs.
3. Determine the most commonly causing interacting pairs of medication in the study population.
4. To determine a Comparison between Demographical data and Numbers of Drug-drug Interaction Pairs.
5. To find out Comparison between Clinical Information Variables and Numbers Drug-drug interactions Pairs.
6. To compare Stockley with Micromedex® and Lexicomp software Drug Checkers of most Frequent DDI Pairs for evaluating the DDI Regarding accuracy.

1.6 Drug-related problem classification schemes:

The primary goal of pharmacological therapy is to find and correct DRPs. Because of differences in DRP definitions and criteria, published literature classifies DRPs in various ways Meyboom et al. (2000). DRP categorizations are also significant for documentation, which is a key aspect in pharmacy practice Currie et al. (2003). As a result, a validated instrument is required.

DRP categories vary in structure and concentrations point. Some classifications distinguish both the reason of a drug-related problem and issue directly, whereas others identify the issue as the cause. In reality, other classifications provide a categorization system for therapies. Most current categories have a hierarchical structure, with higher levels being broadly defined and lower levels becoming more precise. These systems can also accommodate the addition of new subcategories.

In some categorizations, the emphasis is on the patient's point of view and clinical outcome; In another's, the emphasis would be on the prescription, delivery, and medication use processes. There are further classifications geared towards research and designed for pharmacy practice or medication -use assessment (van Mil et al., 2004). Assessment of DRPs categorization instruments is necessary to guarantee that the coding used to address a DRP is explicit. Van Mil et al. proposed five major criteria for DRP categorization verification in 2004, which are as follows:

A. A clarification of the DRP in general, as well as each DRP category.
B. Evaluation of the categorization instrument has been published.
C. Practical and have been utilized in a study presented
D. An organizational structure with distinct groups and subgroups, as well as an open framework that allows for the addition of new issues.

The categorization should focus on the medication use process and consequence, separating the issue from the causation (van Mil et al., 2004).

1.7 Significance and limitations of the study:

Due to multiple related and concurrent diseases, polypharmacy is a common occurrence among the elderly. It's linked to erroneous drug use and, as a result, medication interactions, which could lead to an elevated risk of severe drug reactions and morbidity and mortality in this population (Zeenny et al., 2017).

Patients with many diseases are frequently obliged to attend separate appointments for each of their chronic illnesses, with limited communication between physicians Duncan et al. (2017) found that these people are more likely to have a high treatment burden. Patients admitted to surgery departments can anticipate being exposed to drugs that may interact with their prescription medications or medications used to manage chronic diseases. Antibiotics, analgesics, and CNS depressants are among the most regularly prescribed drugs in surgery departments.

As a result, pDDIs among patients in surgery departments may have different interactions than those among patients in other hospital departments. In surgery departments, little is known about pDDIs (Sánchez-López et al., 2016; Rodrigues et al., 2017).

In another study, Riechelmann et al. discovered 276 potential DDIs among 405 cancer patients in Canada's leading cancer center in Toronto; 9 percent were classified as major interactions and 77 percent as moderate. The majority of these interactions were identified with non-cancer drugs such as antihypertensive and anticonvulsant treatments (Riechelmann et al., 2007). In a similar study conducted in three Palestinian hospitals, the majority of the potential drug-drug interactions identified were classified as major interactions (52.7%), followed by moderate (40.5%), then minor (6.4%), requiring therapy monitoring and, in many cases, benefiting the patient, such as 2 antihypertensive or 2 different antidiabetic drugs prescribed intentionally concurrently as a treatment regime or as per guidelines(Rabba et al., 2020).

Additionally, with numerous theoretically interacting combination therapies on the market, today identifying and controlling potential DDIs has become a difficult undertaking for health care providers and consumers (Bykov & Gagne, 2017). Because DDIs can result in significant and life-threatening situations, preventing or managing difficulties or adverse events falls under the domains of Patient Rights, Safety, and Clinical Governance and Care. The second domain, the Clinical Support Systems domain, covers detailed services essential in the provision of clinical care and includes the timely accessibility of medicines and the effective provision of diagnostic, therapeutic, and other clinical support services and necessary medical technology, as well as a patient medication-related needs (Lourens, 2012).

This study was carried out to assess potential drug-drug interactions and the severity of probable DDIs in hospitalized patients who underwent cardiac surgery. To our best knowledge, there are no published studies that address drug interactions in surgery wards in the Kurdistan region of Iraq.

CHAPTER II

Literature Review

2.1 Background:

Drug interactions caused clinical concerns for the first time in the early 1960s. The Royal Society of Medicine in London hosted the first worldwide symposium on medication interactions and their therapeutic significance in 1965. This issue was the focus of multiple symposia and reviews in important medical publications in the following years, including a particular addition to the Swedish Medical Journal. The Swedish Drug Regulatory Agency, FASS, has obliged the pharmaceutical sector to publish annual reviews of drug interactions in the national formulary since 1970. (Pharmaceutical Specialties in Sweden).

In the initial review, a classification of medication interactions was proposed. according to the mechanisms involved in the interaction between drugs eight classes were defined: absorption, plasma protein binding, transport, effects on receptors, tissue distribution, miscellaneous and renal elimination (Sjöqvist & Böttiger, 2010).

Many medications can interact by boosting (inducing) or inhibiting each other's metabolism, according to research conducted in experimental animals in the early 1960s Burns and Conney (1965) Phenobarbital was utilized as a prototype for enzyme-inducing medicines and was later employed to improve bilirubin glucuronidation in newborn neonates with hyperbilirubinemia. Insecticides in the environment have also been observed to cause drug metabolism in exposure in employees Kolmodin et al. (1969). The possibility that pharmaceuticals could interfere with the metabolism of other medicines taken at the same time was a subject of special concern. Competitive inhibition of drug metabolism happens quickly, whereas induction of drug metabolism is a lengthy process that requires the creation of enzyme(s) (Christensen et al., 1963).

In1963, Christensen et al observed that co-administration of sulphaphenazole (a chemotherapeutic agent) with tolbutamide (an anti-diabetic medication) resulted in hypoglycemia, and suggested that sulphaphenazole inhibited tolbutamide metabolism ‘in a certain way. Sulphaphenazole was discovered to be a selective inhibitor of the cytochrome P450 2C9 enzyme that catalyzes the hydroxylation of tolbutamide thirty years later.

During the 1970s, there was an increase in the number of reports about drug interactions, particularly metabolic drug interactions. In Medline, the total number of medication interaction publications climbed from 43 in 1970 to roughly 1400 in 1980. This increased interest corresponded with the enhancement of science and the development of advanced in vitro systems for studying drug biotransformation processes. Many studies of metabolic drug interactions were based on in vitro discoveries or single-case observations, which added uncertainty and skepticism to the field rather than comprehensive explanation. ‘Unfortunately, there are few, if any, guidelines to allow predictions of which drugs will inhibit the metabolism of others,' according to the seventh edition of Goodman and Gilman's The Pharmacological Basis of Therapeutics (1985), which includes an appendix with over 1700 page references to drug interactions (Sjöqvist & Böttiger, 2010)

In clinical practice, drug-drug interactions, hypersensitivity reactions, adverse drug events, and idiosyncratic reactions have all remained a major issue. Potential drug-drug interactions (pDDIs) have been identified as one of the most commonly occurring challenges that may modify the pharmacokinetics and pharmacodynamics of the medications, hence altering the overall therapeutic response. Identifying pDDIs can help to prevent many adverse effects. Even so, certain circumstances, such as numerous illnesses, chronic conditions, and polypharmacy, may raise the incidence of pDDIs. The effects of pDDIs range from moderate to serious, perhaps lethal occurrences (Murtaza, 2015).

According to studies, up to 27 percent of patients brought to hospitals experience complications as a result of DDIs (Janchawee et al., 2005). According to other studies, DDIs, along with other adverse medication responses, are a serious clinical concern, particularly in hospitalized cardiac patients (Passarelli, M. C. G,2015). Cardiovascular diseases (CVD) continue to be the major cause of death globally (WHO, 2015).

In 2012, an estimated 17.5 million people died from cardiovascular disease, accounting for 31% of all deaths worldwide, with 7.4 million deaths from coronary heart disease with 6.7 million dying from stroke (WHO, 2015). Out of the 16 million deaths of persons under the age of 70 caused by non-communicable illnesses, 82 percent occur in poor and middle-income countries, with CVDs accounting for 37 percent (WHO, 2015).

Disease risk factors include hypertension, hyperlipidemia, diabetes, and other disorders that necessitate numerous pharmacological therapies, whereas lifestyle factors include an unhealthy diet, cigarette use, a lack of physical activity, and stress. Furthermore, treatment for these disorders requires the administration of multiple drugs, which, when paired with elements such as advanced technology, can be rather costly. The probability of potential drug-drug interactions (PDDIs) increases with age, co-morbidities, and alterations in hepatic and renal functioning. Because of the many medication therapies utilized in critical care units such as cardiac intensive care units (CCU), the possibility of a potential drug-drug interaction (PDDI) is quite likely. Combat the patient's complex illness condition, as well as co-morbidities and age, which raises the risk of PDDIs (Shakeel et al., 2016).

Various studies indicate that cardiovascular patients are more likely to have pDDIs than other conditions. Higher pDDI rates in cardiovascular diseases could be due to older age, various treatment regimens, and the pharmacokinetic or pharmacodynamic characteristics of medicines used in cardiology. Cardiovascular medications are more frequently implicated in pDDIs. for instance, Drug-drug interactions involving platelet inhibitors like warfarin, are frequently observed in clinical practice and can cause prothrombin time changes. DDIs with anticoagulant medications like aspirin and clopidogrel frequently result in reinfarction or hemorrhage (Murtaza, 2015).

The definition of DDIs is "two or more medications interacting in such a way that the efficacy or toxicity of one or more medicines is altered. DDI is a major problem in individuals taking multidrug medication. Such interactions may increase the likelihood of hospitalization and raise health-care costs (Mateti et al., 2011). A clinical significance of DDI could either raise a drug's toxicity or decrease its efficacy (Holm et al., 2014). Drug-drug interactions (DDIs) are a subset of adverse drug reactions (ADRs) in which the effects of one drug influence the actions of another, limiting effectiveness or producing toxicity (Roblek et al., 2014).

Besides, Drug interactions aren't always harmful. Therapeutically, some medication interactions are employed. Local anesthetics frequently consist of a combination of lidocaine (or other “-caines”) and epinephrine, which promotes blood vessels to constrict, extending the action of lidocaine in the injection site. After surgery,

reversing medications like naloxone (Narcan) are administered to eliminate the effects of opioids. Several medications are administered concurrently for cancer treatment in order to offer impacts at numerous areas of cancer cell proliferation (Rodrigues, 2019). ADRs are regarded as a major health risk that can harm patients' health or possibly result in death. For instance, Concurrent use of ceftriaxone and lansoprazole at the same time may result in life-threatening arrhythmia (Roden et al., 2016). According to the Centers for Disease Control and Prevention, around 300,000 individuals die from ADRs in the United States and Europe each year (Zhang et al., 2020).

Overall, DDIs account for 1 percent of hospital admissions and 16 percent of ADR admissions. A higher number of this is also linked to more time spent in the hospital and higher treatment expenditures The risk of DDIs rises as the number of drugs given to patients increases. The incidence ranges from 13% when only two medications are prescribed to 82% when seven or more drugs are prescribed (Roblek et al., 2014). In hospitals, at least 15 percent of patients are hospitalized with at least one DDI (Mousavi & Ghanbari, 2017).

According to studies conducted in hospitals, pDDI rates range from 15% to 66%. There is a lack of detailed data on the features of pDDIs in patients hospitalized for CVD (Kovačević et al., 2017). It is estimated that DDI account for around 6-30 percent of all ADRs. Furthermore, ADR from DDI accounts for around 2.8 percent of hospital admissions each year (Sharma et al., 2014).

2.2 Incidence of Drug -drug interactions in Cardiac patients:

Patients who appear for invasive cardiovascular operations are usually taking a number of drugs to treat risk factors for heart and vascular problems. Antithrombotic, hypnotic, and painkiller medications are frequently required during the operation, and new medications are frequently introduced following surgical interventions for reducing the incidence of ischemic events. Aside from these prescribed treatments, the use of OTC medications and supplements is on the rise. The majority of aged patients, for example, take five or more prescribed drugs and One or more supplements, and they frequently have some degree of renal insufficiency. This polypharmacy could lead to drug-drug interactions that alter the balance of coagulant and hemorrhagic events during the surgery

and long-term therapy. Anticoagulant combination, for example, can cause periprocedural bleeding, which has been linked to an increase in long-term complications.

Furthermore, because thienopyridine antiplatelets several to immediate and long-term interventional effectiveness, the breadth of potential interactions with these medications is of concern. The practical hurdles in the field are significant—some drug-drug interactions are likely to exist but are remain unclear due to limited assays, while other interactions have well-described biological effects but appear to be more theoretical because of little to no clinical value. Interventional providers must be aware of the possibility of drug-drug interactions, the associated harm, and the required action, if any, to reduce the risk of drug adverse outcomes (Dunn et al., 2012).

Drug-drug interactions are more common in cardiovascular illnesses than in other diseases. polypharmacy, Older age, and the pharmacodynamics or pharmacokinetic characteristics of medicines used in cardiology may all contribute to the drug-drug DI rate in cardiovascular illness (Assefa et al., 2020). In the USA elder cardiovascular disease patients (age higher than 65 year) had an average of eight concomitant comorbidities and 13 prescriptions. Similarly, studies conducted elsewhere have reported the prescription of a considerable number of various medicines (ranging from 2–24 drugs) to CVD patients. Various etiologies, concurrent comorbidities, complex prescription regimens, and the types of medicines received by cardiovascular diseases patients make them a high-risk category for drug-drug interaction (DDI) (Akbar et al., 2021).

According to studies conducted around the world, the potential of cardiovascular drugs in the participation of DDI is significantly higher (Sharma et al., 2014). Based on another study published by Cruciol-Souza, the overall frequency of pDDIs in cardiology was 49.7 percent 19. Despite the fact that medication interactions have been documented to be widespread in cardiology (Patel et al., 2011). Prevalence of pDDIs in cardiovascular disease patients has previously been found to range from 21.3 to 96.9 percent. A study of hospitalized CVD patients at Ayub Teaching Hospital in Abbottabad, Pakistan, found that 91.6 percent had at least one pDDI (Akbar et al., 2021).

In addition to that, a prospective study conducted in one of India's teaching hospitals, the rate of probable medication interactions among cardiac medicines in hospitalized patients was 30.67 percent. Another study conducted in Nepal to assess the

pattern of DDI among diabetic outpatients discovered that 47.5 percent of drugs potentially interfering with antidiabetics were cardiovascular medications (Sharma et al., 2014).

Moreover, a retrospective cross-sectional investigation on the Cardiology ward of the University Clinical Hospital Center in Belgrade, Serbia, revealed that the total prevalence of potentially relevant pDDI in cardiology was 83.9 percent. The most common probable clinical consequence was the effect on the cardiovascular system (48.5%), renal function and/or potassium (22.3%), hemorrhage (9.5%), poor glucose management (6.8%), and digoxin intoxication (4.6%) (Kovačević et al., 2017).

Besides, according to prospective observational research from Morocco's Mohammed V Military Teaching Hospital. The prevalence of DDIs was estimated to be 68.11 percent, with Kardegic/Plavix (12.22 percent), Kardegic/Heparin (8.33 percent), and Lasilix/Spironolactone (8.33 percent) being the most prevalent (5.83 percent) (Fettah et al., 2018).

In addition, according to a prospective observational study from the cardiology department of a hospital in South India, the prevalence of pDDI was 30.67 percent. The most common possible interactions were aspirin and heparin (29.38 percent) and clopidogrel and heparin (29.38 percent) (7.21 percent). The most typically involved drug classes were antiplatelets, anticoagulants, and diuretics (Patel et al., 2011).

2.3 Drug-Drug Interaction Classification:

DDIs are categorized based on whether the interaction occurs outside or inside the body (Figure 1). Pharmaceutical interactions, also known as incompatibilities, occurring outside the body while pharmacological interactions take place inside it. Pharmaceutical interactions typically occur prior to the administration of medications to the patient (Chaieb et al., 2009).

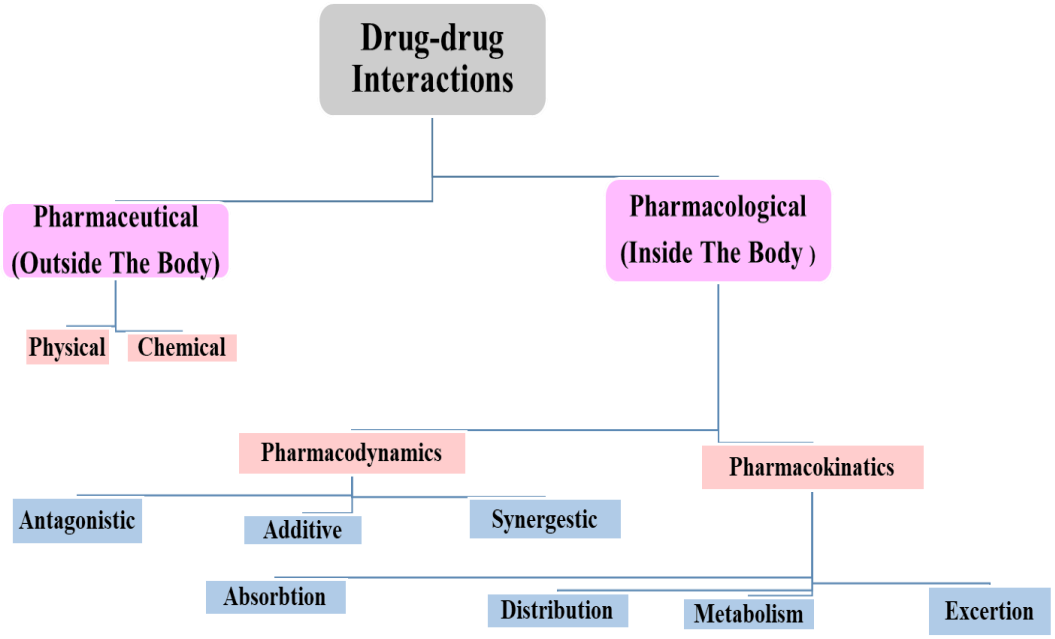

Figure 1:classification of drug interactions (Chaieb et al., 2009)

2.3.1 Pharmaceutical Interactions:

2.3.1.1 Chemical Drug-Drug Interactions:

Pharmaceutical medication interactions are classified as chemical or physical responses. The of calcium chloride and in total parenteral nutrition formulations, often known as TPNs or hyper-alimentation, is an example of a chemical reaction. The two medications may react to create calcium-phosphate, resulting in an accumulation ("snow") in the intravenous (IV) fluid infusion. Persistent seizures (status epilepticus) are a potentially fatal condition that needs the use of medicine to terminate the seizures as soon as feasible. When two regularly used anticonvulsant medications, lorazepam (Ativan), and phenytoin (Dilantin) are mixed in the same IV bag or syringe, they become inactive (Reviewers, 2013).

2.3.1.2 Physical Drug-Drug Interactions:

Physically modifying a pharmaceutical formulation, such as smashing a sustained-release pill, may result in the drug being released faster and/or in greater quantity. Similar issues may arise when food or alcohol is combined with some sustained release drugs. Another physical reaction is the thyroid medicine levothyroxine adhering to IV tubing and

bags. One medicine can affect the formulation of another, for example the combination of propofol emulsion (Diprivan) and diazepam (Valium). Diazepam threatens to destroy the propofol emulsion, leading it to "oil out" and make intravenous administration risky (Trissel et al., 1997).

Drugs can be harmed by environmental factors. Some medications can deteriorate and become less effective as a result of exposure to light. That's why most pharmaceutical bottles are golden or opaque. Medications can be affected in the same way by humidity. Other environmental factors can have an impact on drug absorption. Warming pads, for example, can accelerate the absorption of the opioid fentanyl from transdermal drug delivery (Moore et al., 2012; Gilman, 1985).

2.3.2 Pharmacological Interactions:

More typically, drug-drug interactions are associated with internal body responses or pharmaceutical interactions. Pharmacokinetic interactions and Pharmacodynamic interactions are the two types of pharmacological interactions (Figure 1) (Reviewers, 2013).

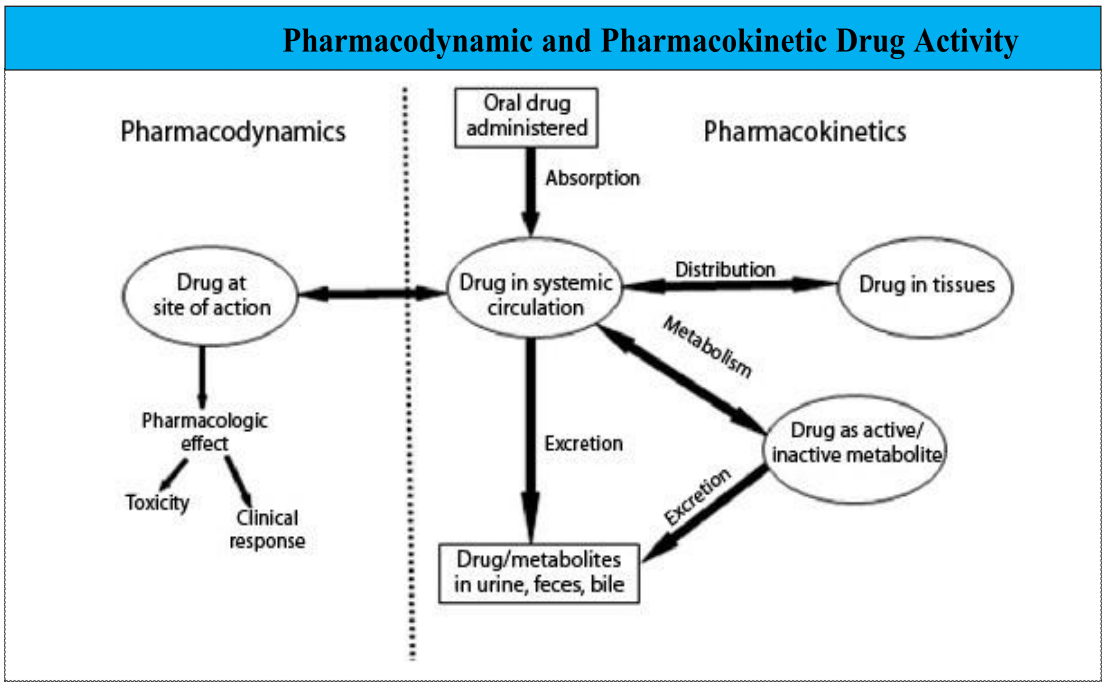

Figure 2: Pharmacodynamic and Pharmacokinetic Drug Activity (Reviewers, 2013)

2.3.2.1 Pharmacodynamic Drug-drug interactions:

The effect of a substance on the body that causes a physiological response is referred to as PD. Medications that interact with protein receptors, such as stimulants for the GABAA receptor, can cause a PD response. Tyrosine kinase inhibitors, which target the protein kinase, may also interact with these molecules in the second messenger system. pharmacodynamics can also happen with enzymes that block platelet activation, such as nonsteroidal anti-inflammatory medications (NSAIDs) and platelet cyclooxygenase Roberts and Gibbs (2018).

Pharmacodynamics Drug-drug interactions happen when a co-administered medicine affects the pharmacodynamics effect of another drug in ways that are not related to their pharmacokinetic effects. These drug-drug interactions, like pharmacokinetic DDIs, occur when two or more medications are delivered to a patient at the same time. The medications can interact either antagonistically or synergistically. DDIs can also happen with medications that work in similar ways, such as decreasing blood pressure On pharmacodynamics responses, pharmacodynamics drug-drug interactions can have additive, synergistic, or antagonistic effects (Vilar et al., 2018 ; Mignat & Unger, 1995).

In response to pharmacodynamic mediated drug-drug interactions, the Emax and EDEC50 can vary. A drop in the EDEC50 causes the dosage response curve to move "leftward," indicating synergism. There is no change in the dose response curve's EDEC50 and an Emax that reflects the aggregate of individual PD responses, indicating additivity. An rise in the EDEC50 demonstrates competitive antagonism by causing a “rightward” shift in the dose response curve (Vilar et al., 2018; Zhao et al., 2010). (A drop in the Emax could be attributed to noncompetitive or uncompetitive antagonism, based on the PD DDI mechanism (Roberts & Gibbs, 2018).

A- Additive:

When the total PD reaction is the sum of the individual PD responses for the individual medications, an additive PD DDI exists. A synergistic drug-drug interaction is one in which the overall PD reaction is greater than the sum of the individual pharmacodynamics responses (Roberts & Gibbs, 2018).

Additive DDIs develop whenever the combined effect of the two 2 medications is greater than the combined effect from each substance when provided separately (1+1=2) (Reviewers, 2013).

For instance, liraglutide is a metabolic hormonal substitute that works as a long-acting glucagon-like peptide-1 receptor agonist to reduce blood glucose, whilst insulin detemir is a long-acting insulin counterpart that likewise works to reduce blood glucose. When the medicines are taken together, the overall glucose-lowering effect is additive and equivalent to the total of the separate PD responses. Other examples of an additive DDI is the interaction between phenprocoumon and nonsteroidal anti-inflammatory medications (NSAIDs). phenprocoumon is a vitamin K antagonism that suppresses vitamin K oxide reductase and hence limits the activation of various clotting factors indirectly. Platelet cyclooxygenase inhibition by NSAIDs reduces platelet activation. Taking these medicines together has the net effect of increasing the risk of bleeding since their anticoagulant actions are cumulative (Roberts & Gibbs, 2018).

B- Synergistic:

When 2 or more medications are combined and their drug-drug interactions are synergistic, the total Pharmacodynamic response can be higher than the sum of the individual PD responses (Roberts & Gibbs, 2018). Antagonistic DDIs develop when the impact of one medication is reduced or eliminated by another (1-1=0) (Reviewers, 2013).

The combination of diphenhydramine and ethanol, for instance, results in synergism in the pharmacodynamic response.

Ethanol increases chloride conductance on post synaptic neurons by acting as a GABAA receptor agonist. Diphenhydramine is a muscarinic acetylcholine receptor antagonist that causes the neuron's positive charge to decrease. This causes a net increase in negative charge throughout the neuron as well as increased activity in addition (Roberts & Gibbs, 2018)

C- Antagonistic:

When one medication diminishes or eliminates the impact of another, antagonistic drug-drug interactions develop. This could happen at the receptor level. Antidotes in

poisoning are based on antagonistic DDIs. Paracetamol (Tylenol) overdoses, for instance, may be managed with acetylcysteine (Mucomyst or Acetadote), a medication that inhibits the harmful effect on the liver by removing toxic metabolites (breakdown products) of paracetamol. Naloxone (Narcan), a narcotic antagonist, is used to treat narcotic intoxication. Antagonistic medication interactions are frequently undesirable; antagonists in that memantine binding requires activation of the NMDA receptor before it can occur. Caffeine, for instance, may diminish the effects of sleep aids, effect of antihypertensive medications may decrease when taken with herbals which used to weight loss (Reviewers, 2013; Horn, 2009).

2.3.2.2 Pharmacokinetic Drug-drug interaction:

PK is described as what the body can do to a medication, or more officially, the flow of medicines through the body, which includes absorption, distribution, metabolism, and excretion (ADME). A medication's PKs are expressed in terms of drug concentration in the blood or plasma vs. time (Figure 3). To have a pharmacologic action, the medication must acquire appropriate concentration at the site of activity (cell receptor site), which is based on ADME. Consider PK to be the time course of drug concentration from a specific dose regimen. Pharmacokinetics can inform us how much of a medicine to provide and how frequently it must be administered in order to get the desired drug concentration (Goodman, 1996; Horn, 2009).

A- Absorption:

The first step in PKs is absorption. In general, medications must be absorbed in order to provide a pharmacologic effect. Medicines administered orally should be absorbed through the gut and/or intestine in achieving the bloodstream and be transported to the site of action. Similarly, medications supplied via intramuscular (IM) or subcutaneous (Sub-Q) injection, as well as medicines administered nasally, sublingually (under the tongue), or via other non-oral routes, must be absorbed from the site of administration. Drugs administered intravenously are injected straight into the bloodstream, skipping absorption, and so have a nearly instantaneous effect. Drugs

administered subcutaneously or intravenously, as well as other non-oral routes, have a slower pharmacological effect than oral medication (Goodman, 1996 ; Horn, 2009).

1. Changes in pH:

A drug's absorption through the gastrointestinal mucosa can be influenced by a number of factors. The first factor is a change in the pH of the stomach. The majority of medications taken orally require a stomach pH between 2.5 and 3 to be digested and absorbed. As a result, medicines that increase gastric pH (e.g., antacids, anticholinergics, proton pump inhibitors [PPI] or H2antagonists) can alter the kinetics of other pharmaceuticals that are coadministered. Indeed, H2 antagonists (e.g., ranitidine), antacids (e.g., aluminum hydroxide and sodium bicarbonate), and PPIs (e.g., omeprazole, esomeprazole, pantoprazole) that increase gastric pH decrease cefpodoxime bioavailability, while on the other hand, which aids in the absorption of betablockers and tolbutamide (Krishna et al., 2009).

Furthermore, because antifungal medicines (e.g., ketoconazole or itraconazole) require an acidic environment to dissolve well, their coadministration with treatments that elevate gastric pH may result in a decrease in both solubility and absorption of antifungal drugs. As a result, at least 2 hours after the administration of antifungal medicines, antacids, anticholinergics, or PPIs may be delivered (Ogawa & Echizen, 2010).

In contrast, medicines that promote a fall in gastric pH (for example, pentagastrin) may have the opposite effect. It is worth noting that the severity of drug-drug interactions caused by changes in gastric pH is primarily determined by the pharmacologic properties of the relevant medicine (Palleria et al., 2013).

2. Chelation and Adsorption:

Chelation in the gastrointestinal tract can cause medicines to produce insoluble aggregates. Chelation is the creation of a ring structure between a metal ion (e.g., aluminum) and a nonmetal ion (e.g., oxygen).

Because of the lack of drug solubility, an insoluble compound is formed by combining an inorganic molecule (e.g., magnesium, iron, and to a lesser extent calcium) and an organic molecule (e.g., anti-infective medication) (Kashuba & Bertino, 2005).

For instance, combining the antibiotic ciprofloxacin (Cipro) with iron or Ca+ supplements (or Ca+ found in milk, yogurt, ice cream, and so on) reduces ciprofloxacin absorption (Reviewers, 2013).

3. Effects of P-Glycoprotein:

Cell carriers such as P-glycoprotein (P-gp) may possibly play a role in drug-drug interaction absorption. P-glycoprotein functions as a "cellular vacuum cleaner," sucking foreign particles out from the cell. Cyclosporine suppresses the immune system in order to prevent the body from rejecting donated tissues. P-gp transports cyclosporine through cell membranes. Some medications and plants, such as St. John's wort, boost the activity of P-gp, forcing cyclosporine to be pumped back out into the intestinal lumen (the inside of the "pipe") and excreted. When St. John's wort and cyclosporine are taken together, there have been reports of organ rejection. P-glycoprotein inhibitors, such as the anti-rejection medicine sirolimus (Rapamune) or the antibiotic erythromycin, might cause increased concentrations of cyclosporine to persist in the body, causing kidney damage (Reviewers, 2013).

4. Changes in Gastric Emptying and Intestinal Motility:

The presence or lack of meals can influence anti-infective absorption through a variety of ways. the absorption of fat-soluble substances can be significantly increase when taken with high fat meals such as griseofulvin, cefpodoxime. erythromycin and penicillin, the increased breakdown of acid-labile drugs like penicillin and erythromycin can be caused by prolonged stomach retention. Because the small intestine is the principal site of medication absorption, alterations in gastric emptying and gastrointestinal motility may have a considerable impact on drug exposure. Faster gastrointestinal motility caused by optokinetic medicines such cisapride, metoclopramide, and domperidone may reduce the degree of absorption of poorly soluble medications or medicine absorbed in a small area of the intestine (Piscitelli, 2011).

5. Effects of Intestinal Blood Flow:

Vasoactive agents have the potential to alter intestinal blood flow, which could have an impact on lipophilic substances' absorption. There's no proof to far, however, that this leads to clinically significant medication interactions (Piscitelli, 2011).

B- Distribution:

Drug competition for protein-binding sites in plasma can result in significant variations in drug distribution. Certain medication classes appear to share a limited number of common binding sites, and one medicine can displace another, sometimes with dramatic results. Normally, 98 percent of warfarin is bound to albumin, leaving only 2% of the total medication in the plasma to be biologically active. If another medicine competing for the same plasma-albumin binding sites decreases warfarin binding from 98 percent to 96 percent, the amount of pharmacologically active warfarin is doubled. This has nearly the same effect on prothrombin time as doubling the anticoagulant dose. By this mechanism, phenylbutazone, oxyphenbutazone, and clofibrate increase the effectiveness of warfarin, and a number of cases have been documented, some of which resulted in fatal hemorrhagic complications (Prescott, 1969).

C- Metabolism:

Many medications' potency and duration of effect are proportional to the pace at which they are bio transformed into physiologically inactive molecules by the liver's drug-metabolizing enzymes. Treatment with a wide range of routinely used medications, insecticides, herbicides, polycyclic hydrocarbons, carcinogens, dyestuffs, and naturally occurring chemicals can boost the activity of these non-specific enzymes several fold Prescott (1969) The cytochrome P-450 enzymes are the most important drug-metabolizing enzymes (Reviewers, 2013).

When a medicine that changes the activity or synthesis of a CYP enzyme is combined with a drug metabolized by the CYP enzyme, Metabolism DDIs can arise. The “substrate” is the medication that is metabolized by the CYP enzyme (think of it as the “victim” that is metabolized by an enzyme). Inhibitors are drugs that inhibit the activity of CYP enzymes and boost the effect of the substrate medication. Inducers are drugs that

cause the creation of higher amounts of enzyme and hence reduce the impact of the substrate medication. Theophylline, an asthma medication, is a CYP1A2 substrate. If a patient with therapeutic theophylline levels starts taking cimetidine (Tagamet), which is used to treat gastroesophageal reflux disease (GERD, heartburn), theophylline amounts may rise to toxic levels because cimetidine suppresses the function of CYP1A2 and theophylline is digested more slowly. In contrast, if a patient with therapeutic blood levels of theophylline started smoking cigarettes, theophylline concentrations may fall to subtherapeutic levels because nicotine stimulates the body to break down theophylline. to increase the production of CYP1A2, allowing theophylline to be digested more quickly. In general, inhibition DDIs occur within hours or a day or two; induction Drug-drug interactions take longer, days to a couple of weeks, because the inducing drug causes the body to generate more enzyme (Reviewers, 2013).

D-Excretion:

Drugs and their metabolites must be removed from the body, which can happen in a variety of ways. The lungs have a critical role in the elimination of inhalational medications, whereas the liver, kidney, and gastrointestinal system play a role in the elimination of parenterally delivered pharmaceuticals (Corrie & Hardman, 2011).

The kidney is in charge of eliminating most medicines and their metabolites. DDI can happen at the active tubular secretion level, when two or more medicines use the same transport mechanism. When the renal excretion of the antiproliferative medication is hindered, NSAIDs frequently trigger the emergence of toxic effects of methotrexate. Similar rivalry between other pairs of medications, on the other hand, can be used for therapeutic benefits; for example, probenecid can enhance the serum concentration of beta-lactams, delaying their renal elimination and thereby saving on dosage. drug-drug interaction can happen during tubular reabsorption as well. Many medications move through tubular cells by diffusion when they are in an ionized form in the urine. Pharmacologically induced changes in urine pH modify the degree of ionization of certain medicines and may thus impair reabsorption from the renal tubule (Saha, 2018).

2.4 Factors that increase the Risk of Drug-drug Interactions:

The occurrence of prospective DDIs is influenced by a variety of factors. Prescriber issues such as multidrug prescriptions by several prescribers, insufficient knowledge of prescribers' on drug-drug interactions, or poor recognition of the significance of DDIs by doctors are among the risk factors significantly associated with Drug-drug interactions (Ayenew et al., 2020).

2.4.1 Polypharmacy:

Disease therapy is generally accompanied by the use of multiple drugs; however, this may raise the risk of Drug-drug interactions. According to recent study from the United States, the percentage of people taking 3 or more medications has risen from 11.8 percent in 1988–1994 to 20.8 percent in 2007–2010. In addition, during this time span, the proportion of patients using five or even more medications climbed from four percent to ten percent (Percha & Altman, 2013).

Goldberg et al. reports that the percentage of DDI risk in patients who take two drugs was 13 percent, in patients who took 5 drugs 38 percent, and in patients who took 7 or more drugs 82 percent. The study concluded that taking 3 or more medicines, as well as patients over the age of 50, posed significant risks for adverse Drug-drug interactions (Goldberg et al., 1996).It is vital to assess and evaluate polypharmacy-exposed patients; they must be constantly managed to avoid DI-related complications (Bjerrum et al., 2008).

2.4.2 Age:

Age is regarded as a major risk factor for DDIs. drug-drug interactions can occur at any age, but the risk increases in older people due to the increased frequency of polypharmacy. 25 per cent of older out-patients who are taking a greater than1 medicine have been shown to suffer adverse drug reactions or to have a decreased pharmacological action of drugs, most likely as a result of DDI, in the Netherlands. Diagnosis Clinics of diminished cognition, functional dependence, or both. The prevalence rate of DDIs rises after the age of 44, with patients over the age of 74 having the highest incidence. DDIs, on the other hand, are prevalent in very children (age 5 years) because of their enzymatic metabolism system is immature (Aparasu et al., 2007).

2.4.3 Drug-drug interactions dependent on the patient's illness state:

DDIs are frequent in people with cardiovascular disease, HIV infection, psychiatric patients, and kidney and liver failure (CKD, cirrhosis). Because this type of patient takes a variety of medications, their kidneys and liver may be unable to excrete and metabolize them. As a result, the incidence of Drug-drug interactions in this patient group could be high (Ayenew et al., 2020).

Prescriptions for patients with cardiovascular disease and concomitant diseases were shown to have the highest average number of drug interactions, followed by prescriptions for patients with cardiovascular disease (without comorbid conditions) (Akbar et al., 2021). A significant proportion of people with chronic kidney disease who were being treated conservatively had potentially dangerous drug interactions in their prescription medications (Marquito et al., 2014).

Congestive heart failure is another illness linked to an increased incidence of DDIs (CHF). The medications used to treat congestive heart failure seem to be critical for pharmacological advancements, therefore doctors cannot rule them out. Overtreatment is unavoidable in the treatment of Congestive heart failure, and individuals may incur adverse effects such as hypotension, hyperkalemia, and kidney failure (Cleland et al., 2000). Furthermore, people with cancer commonly take a variety of medications for treating cancer, drug-induced toxicity, cancer-related disorders, and other complications. As a result, individuals are at risk of developing Drug - drug interactions (Reviewers, 2013).

2.5 Tools for DDIs:

Drug related problems identification and monitoring could save lives while also improving patient quality of life and lowering health-care expenses (Abraham, 2014). Programs and electronic databases for drug interaction monitoring were developed to help clinicians uncover critical medicine interactions and so enhance patient safety (Turgeon & Michaud, 2016). There were considerable disparities between computerized database subjective observations, particularly between DDIs The quality and reliability of resources that are often used must be taken into account by professionals (Patel & Beckett, 2016).

Patel and Beckett (2016) conducted research in which they attempted to assess 7 drug information resources specially developed for analyzing drug interactions for scope (the lack or presence of a response to a drug information question), completeness (the completeness of an answer), ease of use (the number of hypertext links required to reach the required response), and also to decide the content's reliability across the 7 resources. They discovered that Clinical Pharmacology Drug Interaction Report (97 percent), Lexicomp Interactions (97 percent), and Micromedex Drug Interactions (93 percent) had higher scope scores than other resources. When compared against Clinical Pharmacology Drug Interaction Report, Facts and Comparisons answers, Shockley's Drug Interactions Analysis and Management, and Drug Interaction Facts, Lexi comp ranked the highest for overall thoroughness and consistency (Yin et al., 2007 ; Patel & Beckett, 2016)

According to Patel and Beckett (2016) Lexi comp Interactions and Stockley's Interactions may be the best resources for determining the mechanism of a potential DDI, but Micromedex Drug Interactions may be more useful for identifying potential clinical effects. Micromedex® has been demonstrated to be a reliable tool for detecting medication interactions with high sensitivity and specificity. (Kheshti et al., 201) ; Roblek et al., 2015) Drug-drug interactions are classified by Micromedex® based on their onset, severity, and documentation (Bista et al., 2009).

The onset of medication interactions might be rapid, with the effect appearing within 24 hours of administration, or it can be delayed, with the effect appearing after 24 hours (Bista et al., 2009).

Micromedex categorizes drug-drug interactions as major (life-threatening and requiring medical intervention), moderate (may need medical intervention), or minor (has a small effect and frequently does not demand medical intervention) (Sharma et al., 2014),(Nusair et al., 2020).Micromedex categorizes encounters as excellent, good, fair, poor, or unlikely in terms of documentation. Controlled clinical trials are accompanied with excellent documentation(Sharma et al., 2014).

Good documentation refers to interactions that are supported by research other than well-controlled trials; fair and bad documentation refer to interactions that are not supported by good evidence. Unlikely documentation is devoid of pharmacological support (Sharma et al., 2014).

However, methods that analyze multiple medication pairings in a sequence frequently inform doctors of non-significant interactions, which can be upsetting, time-consuming, and mentally tiring. As a result, health care professionals may choose to disable the alert feature or disregard it entirely (Turgeon & Michaud, 2016). According to a systematic review published in 2014 aimed was to examine the usability and applicability of commercially available data bases that estimate the prevalence of probable DDIs A total of 3766 papers were found using a systematic search. The analysis included 38 publications after applying inclusion and exclusion criteria. Micromedex® Drug-Reax was the most widely used software in the included research, and some authors suggest that it is the most reliable due to its great sensitivity (Roblek et al., 2015).

. Micromedex® has been demonstrated to be a reliable tool for detecting medication interactions with high sensitivity and specificity (Kheshti et al., 2016 ; Roblek et al., 2015). Another study done by Kheshti et al. (2016) aimed to compare the ability of five commonly used DDI systems to detect clinically significant DDIs. demonstrated that Micromedex showed the highest specificity (0.78). and received the second highest total score (330) Barron's studied The accuracy, comprehensiveness, and ease of use of drug interaction software used with personal digital assistants (PDAs) which included iFacts, Mobile Micromedex, LexiInteract, Mosby's Drug Consult, Clinical Pharmacology OnHand, Epocrates Rx, Handbook of Adverse Drug Interactions, Mobile PDR, and Tarascon Pharmacopoeia Deluxe, demonstrated that iFacts and Micromedex received the highest accuracy score (390 out of 400). And they also found that Facts and Micromedex were among three gold standards regarding Clinically important drug interactions(Barrons, 2004) Despite the fact that electronic databases must be up to date on a regular basis and that some databases require improvement, they remain a valuable resource for health care professionals in order to improve patient outcomes and reduce hospital stays.

2.6 Clinical Pharmacist Role in the Prevention of Potential Drug Interactions:

Clinical pharmacists have specialized training in therapeutics and help patients and providers with complete medication management (includes doctors and also members of health care teams). medication appropriateness, patient satisfaction adverse

drug reactions (ADRs), adverse drug Vevents (ADEs) health related quality of life, and Economic, are all consequences of pharmacist intervention.

The identification, resolution, and avoidance of DRPs are all part of clinical phar macy's core practice. In addition, Pharmacists are crucial in the documentation of adverse drug reactions (ADRs) (Dunn et al., 2015). moreover, clinical pharmacists can analyze DRPs in a variety of settings, including hospitals multidisciplinary teams, nursing homes, and patient care (Viktil & Blix, 2008). However, in hospital settings, the pharmacist's contribution in recognizing and resolving clinically critical DRPs is particularly valuable. Within hospitals Cooperative for pharmacotherapy is a practice of clinical pharmacy that entails collaboration between doctors on a patient's drug therapy. As a result of the teamwork, the overall quality of life and medication therapy of patients are enhanced (Gattis et al., 1999).

This can be understood by pharmacists' substantial medical knowledge, as they are able to link the patient's symptoms to the pharmacological therapy's potential side effects. Clinical pharmacists also limit the occurrence of ADRs by avoiding medications with probable side effects in vulnerable patients (Dunn et al., 2015).

In reality, pharmacists' responses to DRPs are used to analyze their participation in drug therapy optimization, even though this assessment includes measuring the amount of drug related problems handled nor avoided, as well as measuring patient clinical outcomes (Viktil & Blix, 2008).During the 12-month follow-up period, Hanlon et al found that pharmacist revision of the patients' medicines, as well as conversations with doctors, reduced improper prescription prescribing and ADRs (Hanlon et al., 1996). Clinical pharmacists also advise patients prior to release in order to detect DRPs after and during their stay in the hospital. They could identify and address medication inconsistencies, as well as screen for non-adherence and predicted adverse events after discharge, using this method (Schnipper et al., 2006).

In furthermore, assessing the frequency of highlighting risk factors and clinically important drug-drug interactions of the patients throughout consultations is a crucial strategy used by pharmaceutical care to reduce DRPs (Aparasu et al., 2007). Clinical pharmacists have discovered an unique effect in heart failure patients. In a single-center, randomized clinical trial of 180 patients with heart failure (Milfred-LaForest et al., 2013).

investigated the efficacy of pharmacist participation in heart failure rounds. After 6 months, the team with pharmacist engagement had a significantly lower composite of all-cause mortality and heart failure events (4 events vs. 16 events [all-cause mortality or heart failure]; p = 0.005). The management of inpatients and outpatients with heart failure by pharmacists has resulted in fewer hospitalizations and readmissions (Dunn et al., 2015).

The Heart Failure Society of America and the ACCP Cardiology Practice and Research Network recently collaborated on an opinion paper that highlighted and endorsed the role of pharmacists in multidisciplinary heart failure teams (Dunn et al., 2015). Nurses and clinical pharmacists in direct patient care roles, supervised by a physician, are used in Kaiser Permanente of Colorado's collaborative practice approach. In patients with coronary artery disease who were followed in the program for more than 3 years, this model reduced all-cause mortality (adjusted hazard ratio: 0.24; 95 percent confidence interval: 0.20 to 0.29; p lower than 0.001) or coronary heart disease–related mortality (adjusted hazard ratio: 0.27; 95 percent confidence interval: 0.22 to 0.34; p lower than 0.001).

Patients who were entered within 90 days of their coronary incident ("early exposure") had reduced all-cause mortality across a 10-year follow-up period than patients who were not enrolled within 90 days (4.7 percent early vs. 8.6 percent delayed, 16.4 percent intermittent, and 46.9% none; p lower than 0.001) (Merenich et al., 2007).Within 3 to 6 months of discharge for a coronary event, patients are routinely enrolled in a nurse-managed cardiac rehabilitation program, followed by enrollment in a pharmacist-managed program. The objectives were to improve the adoption of evidence-based medicines, assist in the monitoring and control of disorders that raise CVD risk (such as hypertension, hyperlipidemia, diabetes, and substance misuse), and offer information to patients and other team members (Sandhoff et al., 2007).

Medication adherence has also been shown to improve when pharmacists are involved. Ho et al. assessed a comprehensive intervention to promote medication adherence in the Veterans Affairs health system, which included pharmacist-led medication reconciliation, education, and collaborative care between pharmacists and clinicians. Patients who received the intervention had a higher rate of adherence to cardiovascular drugs (clopidogrel, beta-blockers, statins, and angiotensin inhibitors) than

those who received normal care (73.9 percent vs. 89.3 percent; p = 0.003) (Ho et al., 2014). Klopotowska et al. also found that after hospital pharmacist assistance, adverse medication events dropped considerably (Klopotowska et al., 2010).

2.7 Previous Studies in The Cardiology Setting:

In 2020 A cross-sectional study was conducted in three governmental Palestinian hospitals: aimed to determine the potential DDI prevalence in the departments of surgery. a total 502 patients were included in this study The incidence of DDIs interactions among the patients admitted to surgery wards in three Palestinian hospitals was 56% (Rabba et al., 2020). A prospective study was conducted in 2018 with the goal of determining Drug - drug interactions in confirmed cases to the pulmonary and cardiology units for a year. A total of 1150 individuals were enrolled, with 685 of them being cardiovascular patients as well as 465 being pulmonary cases. The most common diagnosis for cardiac patients (31.48 %) is hypertension, followed by angina with diabetes mellitus (21.18 %). While asthma is typically diagnosed in pulmonary patients (21.73 %). There were 856 potential DDIs detected in cardiac patients and 675 potential DDIs observed in pulmonary patients. Aspirin and clopidogrel were the most prevalent drug combinations that induced DDI combination of Ranitidine-theophylline was the most prevalent in 245 cardiac patients, with 195 drug interactions (Ramalingam et al., 2018).

Prevalence of pDDIs in cardiovascular disease patients has previously been found to range from 21.3 to 96.9 %. A study of hospitalized CVD patients at Ayub Teaching Hospital in Abbottabad, Pakistan, found that 91.6 % had at least one pDDI (Akbar et al., 2021). According to a prospective study conducted in one of India's teaching hospitals, the rate of probable medication interactions among cardiac medicines in hospitalized patients was 30.67 % (Patel et al., 2011). Another study conducted in Nepal to assess the pattern of DDI among diabetic outpatients discovered that 47.5 % of drugs potentially interfering with antidiabetics were cardiovascular medications (Sharma et al., 2014).

Moreover, a retrospective cross-sectional investigation on the Cardiology ward of the University Clinical Hospital Center in Belgrade, Serbia, revealed that the total prevalence of potentially relevant pDDI in cardiology was 83.9 %. The most common probable clinical consequence was the effect on the cardiovascular system (48.5%), renal

function and/or potassium (22.3%), hemorrhage (9.5%), poor glucose management (6.8%), and digoxin intoxication (4.6%) (Kovačević et al., 2017). Furthermore, according to prospective observational research from Morocco's Mohammed V Military Teaching Hospital. The prevalence of DDIs was estimated to be 68.11%, with Kardegic/Plavix (12.22 %), Kardegic/Heparin (8.33 %), and Lasix/Spironolactone (8.33 %) being the most prevalent (5.83 %) (Fettah et al., 2018). In addition, according to a prospective observational study from the cardiology department of a hospital in South India, the prevalence of pDDI was 30.67 %. The most common possible interactions were aspirin and heparin (29.38 %) and clopidogrel and heparin (29.38%) (7.21 %). The most typically involved drug classes were antiplatelet, anticoagulants, and diuretics (Patel et al., 2011).

CHAPTER III

Materials and Methods

3.1 Study Design:

A retrospective study was carried at Surgical Specialty Hospital -Cardiac Center using a quantitative descriptive study methodology. The data for this study came from the archives of inpatients who underwent cardiac surgery between January 2020 and February 2021.The study flow is presented graphically in Figure 3.

Figure 3: Schematic Representation of the Research Process.

3.2 Participants / Population & The Sample / Study Group:

3.2.1 Study Setting:

This research study was conducted at surgical specialty hospital cardiac center which is the first and biggest center for cardiac surgery and located in Erbil city, it's a capital city of Kurdistan region of northern part of Iraq.

3.2.2 Participants and Population of the Study:

The study participants and population included only inpatients who underwent cardiac surgery at a surgical specialty hospital cardiac center. The hospital has 100 beds, four operating rooms, two cardiac catheterization units, and comprehensive diagnostic, laboratory, and CT angiography departments. Pediatric, medical, and surgical specialties,

outpatient departments, a primary Percutaneous coronary intervention (PCI) clinic, and a coronary care unit with primary PCI facilities, as well as critical care units, respiratory care units, and a dental department are among the clinical departments. The typical yearly utilization in this hospital is 10,000 patient visits, 750 surgeries, 3,000 catheterizations, and 2,500 CT angiography tests.

3.2.3 Sample size and Sampling of the Study:

The total population of patients who were hospitalized for cardiac surgery at a surgical specialty hospital cardiac center were 750 patients from January 2020 till January 2021.The required sample size was 260 for this study that was calculated by using the following equation for observational studies:

Minimum Sample Size $(SS) = Z2 \times p \times (1 - p)/c2$, where Z represents the confidence level (for example, 1.96 confidence level for 95%), p is the choice of estimated percentage (assigned 50% for the most conservative assumption) and c is the desired level of precision, i.e. 0.05 (Nourı et al., 2018). After adjusting for incomplete files and exclusion criteria a totalsample size of 300 patient files were randomly extracted. These files were selected by using simple random sampling technique.

The samples were selected besed on these inclusion and exclusion criterias ;

3.2.3.1 Inclusion

The study comprised the following patient files:

Patients hospitalized at Surgical specialty hospital cardiac center during the period from January 2020 to January, 2021.

1. Prescriptions with 2 or more drugs.
2. Patients aged 18 years and older.
3. Patients underwent for CTS surgery

3.2.3.2 Exclusion

Patients who their files were uncompleted.

3.3 Data Collection Tools/Materials:

3.3.1. Data collection Tools:

Data were obtained using a data collection form (appendix C), which included demographic information on the patients, such as Age, Gender, length of stay, type of operation, comorbidities, drug list including time and date of administration, number of drugs receiving during hospitalization and generic names of drugs.

3.3.1.1 Demographic Variables:

A total of 300 patients were hospitalized at Surgical Specialty Hospital Cardiac Center during the period of this study. Data were obtained using a data collection form (appendix C), which included demographic variables on the patients, that were Age and Gender.

3.3.1.2 Clinical Information Variables:

In Clinical information variables, Data were obtained which included on the patients, which were length of stay, type of operation, comorbidities.

3.3.1.3 Clinical Drug Information Variables:

Clinical Drug Information Variables were obtained using a data collection form (appendix C), which included drug list including time and date of administration, number of drugs receiving during hospitalization and generic names of drugs.

3.3.2 Data Collection Materials

3.3.2.1 Micromedex®×:

Micromedex®× 2.0 was used to identify and analyze the potential drug-drug interaction. With easy-to-understand clinical information, this application supports healthcare providers in making safer and faster decisions. This application was created to give healthcare professionals with evidence-based clinical information, and it features various functionalities as well as critical information on drug-drug interactions (Sivva, Divya, 2015).

Micromedex® is an electronic database that includes a DDI portion known as the Drug-REAX System. When you enter a medication list, it identifies any potentially dangerous drug interactions based on severity, onset, and documentation status. Micromedex categorizes DDI as major, moderate, or minor based on severity:

Major: Potentially life-threatening; requires medical intervention to minimize or prevent the serious adverse effects)

Moderate: Results in potential deterioration of patients' clinical condition and may require an alteration in therapy.

Minor: The effects are usually mild and may not require change in therapy.

On the basis of documentation status, it additionally categorizes possible DDI as excellent, good, fair, poor, or unlikely:

Excellent: The existence of the drug interaction has been clearly established by the controlled studies.

Good: The existence of drug interaction is suggested by documentation, but well-controlled studies are lacking.

Fair: Available documentation is poor.

Poor: Documentation is scant; however, the possibility of a clinical conflict exists.

Unlikely: Documentation as well as a sound pharmacological basis is lacking.

Regarding the onset of drug interaction, it also categorizes as

Rapid: the effect appearing within 24 hours of administration,

Delayed: the effect appearing after 24 hours

Each patient's medication list was entered into the Micromedex® software program, and a report was generated detailing the potential drug interactions as well as categorizing each interaction as major, moderate, or minor based on severity, onset, and documentation status.

3.3.2.2 Lexi-Interact:

Lexicomp drug interaction checker was used to recheck the severity of top identified drug interaction pairs by Micromedex. This is produced by Wolters Kluwer Health. Lexi-comp is the most comprehensive medication resource, with contents addressing all patient demographics and clinical disciplines including p Lexi-comp

includes more than 25 items, including six source information of prescription and over-the-counter drug monographs, two books on international monographs, and single books on herbal monographs, patient education for adult and pediatric populations, pregnancy and lactation, toxicology, drug allergies, lab and diagnostic tests, and pharmacogenomics.

A pill identifier, an oral and topical medication interaction tool, more than 100 clinical calculators, and two intravenous-drug interaction tools are among the interactive features. pharmacy, internal medicine, cardiology, cancer, psychiatric, anesthesiology, and so more.

3.4 Ethical Considerations:

3.4.1 Permission:

Ethics approval for this study was obtained from Hawler Medical university (HMU) before the study was commenced and permission was granted to conduct the study (HMU) approval number: 932.HMU.ECPH.2021 (see appendix A). Permission to conduct the study at the surgical speciality hospital cardiac center was asked for and granted by the hospital manager and head of surgery department (See Appendix B).

3.4.2 Informed consent:

Because the files were reviewed retrospectively, informed consent was not required for this research.

3.5 Data Analysis Plan:

3.5.1. Data Management:

A total of 300 patients were collected at Surgical Specialty Hospital Cardiac Center ,presents how the data manged during analysis. Among Demographic variables, the Age variable was not normally distributed. That is why the Researcher uses Median and Interquartile Range (IQR) to present the descriptive Statistics of Demographic Variables. The age was between 19 to 90 years' old with median 59, which was divided into four groups, 19 - 35 years old ,36 - 55 years old and ≥ 56 years old respectively.

Morever, There were Drugs prescribed for patients and it had a range of drugs that was between 4 to 19 drugs with median 12. In addition to that, the Number of prescribed

Drugs were divided in to three groups that they were ≤ 7 Drugs, 8 - 14 Drugs and ≥ 15 Drugs. The range of staying in the Hospital was 3 to 15 days with median 7. That was divided in to two groups, they were > 7 days and ≤ 7 days.

To evaluate the DDI monographs' quality, 29 of most repeated drug interaction pairs that were identified by Micromedex were analysed by lexicomp program, a hard copy of Stockley's Drug Interactions Pocket Companion 2015 (van Mil, 2015) used as major reference in identifying drug-drug interaction pairs. Furthermore, each pair interaction was analyzed by lexicomp program and then they were compared with Stockley's Drug Interactions. In this manner, the number of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) results for each program were discovered. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the software programs were then assessed in order to measure software accuracy in identifying DDI.

The software's sensitivity was defined as its ability to correctly detect clinically significant interaction pairs. The ability of the software to reject clinically irrelevant interaction pairings was described as specificity. The PPV indicated the possibility that when the software recognized a DDI, it was a clinically significant interaction. The NPV indicated the possibility that when the software ignored a DDI, it was a clinically insignificant interaction. The accuracy score was calculated by adding the values of sensitivity, specificity, PPV, and NPV and multiplying the total by 100 (Vonbach et al.,2008).

3.5.2 Statistical analysis:

The collected data was entered in Microsoft Office Excel 2016 and Statistical Package for the Social Sciences (SPSS) statistical software version 23. Descriptive statistics were employed to evaluate catigorical data, which was presented in frequency and percentage. In addition, certain categorical data is shown in graphs using Microsoft Office Excel 2016. Regarding the comparisons between variables Mann-Whitney U test and That Kruskal-Wallis Test were used. A p-value of < 0.05 was considered as statistically significant.

CHAPTER IV

Results

4.1 Demographic variables:

Table 1 shows that the socio-demographic characteristics of patients. Nearly two third of the participants (N = 177,64.3 %, median = 65, IQR = 10) were above 56 years old. The second highest group was the age between 36 – 55 years old and which was almost one-third of participants. That was (N = 103,34.3%, median = 51, IQR = 7). The Lowest group was the age group of 19 -35years old which was (N = 20. 6.7%, Median = 30, IQR = 7). The Majority of the study participants were male (219,73 %).

Table 1: Demographic Variables of Patients

Items		Frequency	%	Median	Min/Max
Age of Participants				59	
Age Groups of Patients	**19 - 35 years old**	20	6.7		19 / 35
	36 - 55 years old	103	34.3		36 / 55
	≥ 56 years old	177	59.0		56 / 90
	Total	**300**	**100 %**		
Gender Of Patients	**Male**	219	73 %		
	Female	81	27 %		
	Total	**300**	**100 %**		

4.2 Clinical Information Variables:

The patients were under went various types of Surgery which they were Other Surgery, Coronary Artery Bypass Graft (CABG), Aortıc Valve Replacement (AVR), Mitral valve replacement (MVR), CABG+MVR, Bentall, DVR, ASD, Post-CABG and CABG+AVR. The Duration were divided into two Groups. Additionally, the patients were included in this study were diagnosed with comorbidities; they were Hypertension, Diabetes Mellitus, Dyslipidemia, Respiratory Diseases and Thyroid Diseases.

Table 2: Clinical Information Variables of Patients

Items		Frequency	%	Median (IQR)	Min/Max
Type of	**Other Surgery**	**15**	**5 %**		
Operations	**CABG**	203	67.7 %		
	AVR	19	6.3 %		
	MVR	16	5.3 %		
	CABG+MVR	10	3.3 %		
	Bentall	8	2.7 %		
	DVR	5	1.7 %		
	ASD	7	2.3 %		
	Post-CABG	5	1.7 %		
	CABG+AVR	4	1.3 %		
	Total	**300**	**100 %**		
No. of Hospital stay				7 days	
Groups of	**> 7 days**	118	39.3	6 (1)	3 / 6
Hospital Stay	**≤ 7 days**	182	60.7	8 (2)	7 / 15
	Total	**300**	**100 %**		

Table 2 demonstrates the clinical information of the patients that were types of operation and groups of hospital stay. The CABG (67.7 %) was one of the highest percentages among types of operation which were done for the patients and the CABG + AVR (1.3%) was the lowest percentage. Apart from that, the groups of staying in the hospital were nearly two third of participants (182, 60.7 %) were stayed for 7 days and or more days stayed in the hospital.

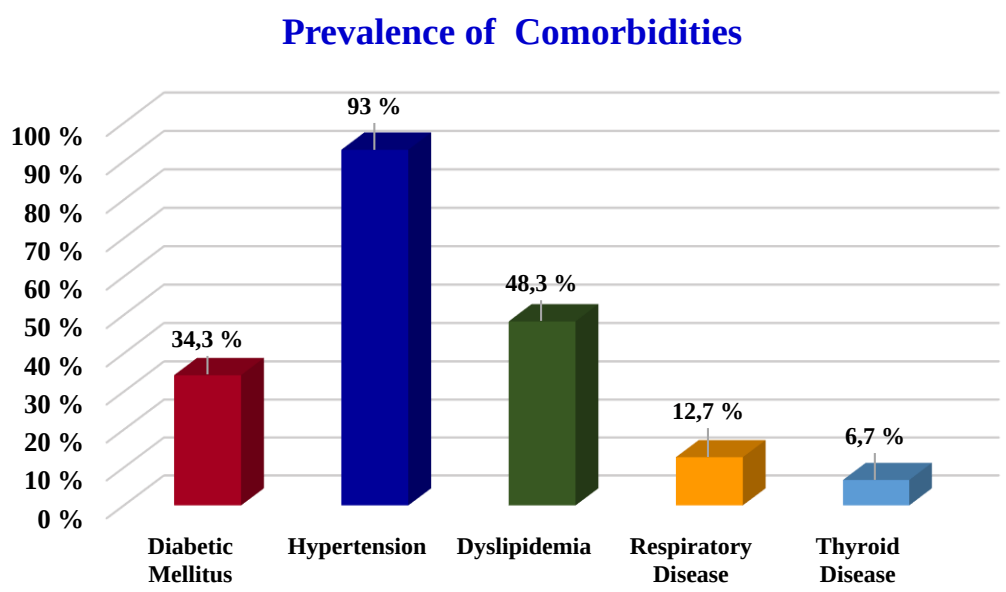

Figure 4 : The Prevalence of Comorbidities.

Figure 4 reveals the prevalence of all five Comorbidities were also found which were Hypertension, Diabetic Mellitus, Dyslipidemia and Respiratory diseases which were reported in the Hospital. Among Comorbidities, Hypertension was the highest prevalence of comorbidities which was majority (N = 279, 93 %), almost half of them (N = 145 ,48.3 %) were had two Dyslipidemia. The Respiratory Disease and the Thyroid Disease were the lowest prevalence (N = 38 ,12.7 %) and (N = 20 ,6.7 %) Respectively.

4.3 Clinical Drug Information Variables:

There were total of 3706 drugs prescribed for all 300 patients with median (IQR), 12 (3). Drugs categorized into three groups. The Number of drugs variable was not Normally distributed, so the Researcher uses Median and Interquartile Range (IQR) to present the descriptive statistics of some clinical drug ınformation variables, the rest of variables were presented in Graphs. Regarding drug drug interaction pairs, of 300 participants' 292 of them had at least one DDI a total of 3680 pairs were detected in with median (IQR) 9(6) In addition to that, the Researcher presented the severity of drug-drug ınteraction of pairs, the type of onset of drug-drug ınteraction, the mechanism of drug-drug ınteraction visually. Overall, there were 3080 times drug-drug were interacted.

Table 3: Groups of Prescribed Medications.

Items		Frequency	%	Median	Min/Max
NO. of Prescribed Medication				**12 Drugs**	
Groups of Prescribed Medication	**≤ 7 Drugs**	15	5.0		4 /7
	8 - 14 Drugs	213	71.0		8 / 14
	≥ 15 Drugs	72	24.0		15 / 19
	Total	**300**	**100 %**		

Table 3 shows that the Groups of Prescribed Medications. The number of prescribed medication was divided into three groups. Nearly more than two third of the participants (213,71 %) and (Median = 12, IQR = 3) was 8 – 14 drugs prescribed for them. The group of ≥ 7 was the lowest (15, 5 %) group and (Median = 7, IQR = 2).

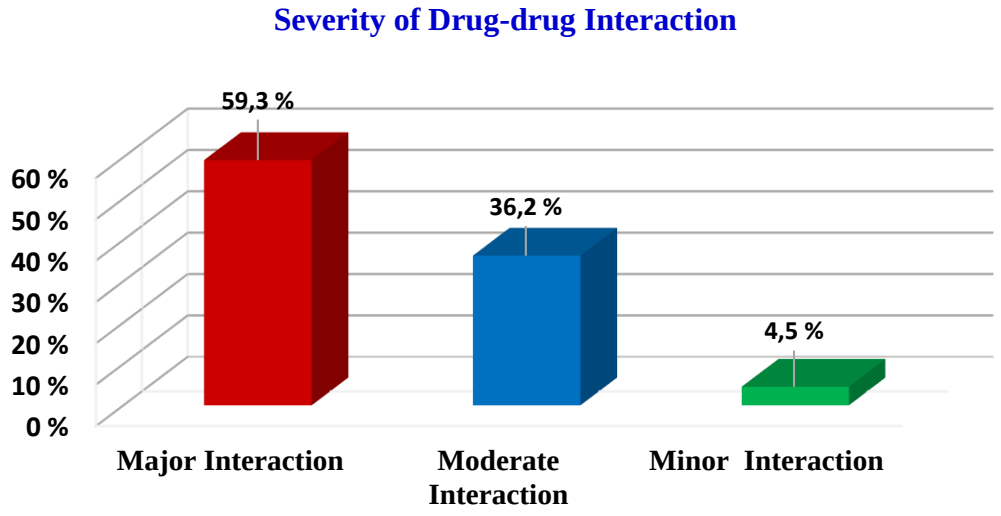

Figure 5: Severity of Drug-drug Interaction.

The Figur 5 demonstrates the severity of drug-drug ınteraction of pairs which were prescribed for the patients. The Major interaction was almost two third (59.3 %) while the

Minor interaction was the lowest percentage (4.5 %) among the type of Severity of Drug-drug Interaction.

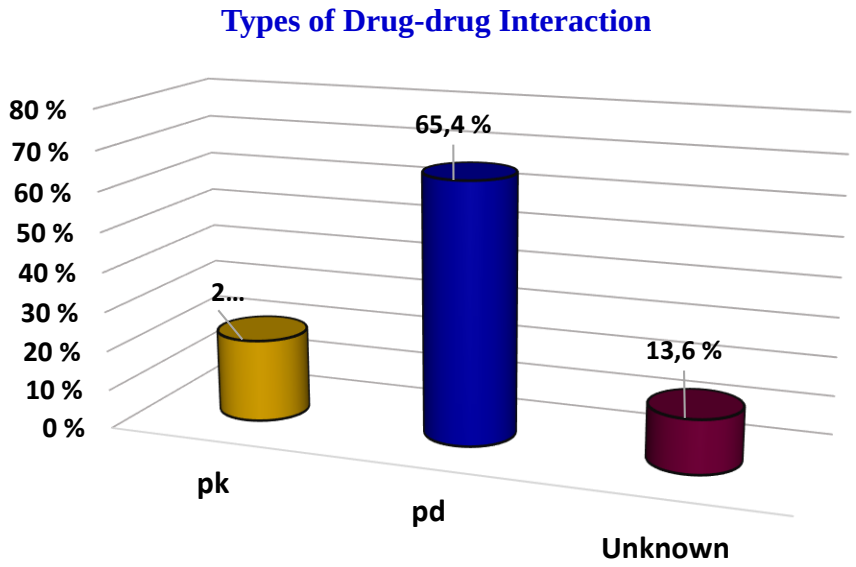

Figure 6: Types of Drug-drug Interaction.

In Figure 6 reports that the types of drug-drug ınteraction. That the pharmacodynamics (pd) type was the highest which was two third (65.4 %) of Types of drug-drug ınteraction and pharmacokinetics (pk) was one fifth (21 %) of drug-drug ınteraction.

Table 4: Identified Top Ten of Most Repeated Major Interaction Pairs.

NO.	Drug-Drug Interaction Pairs	Frequency	%	Type of onset	Type of Interaction	Mechanism of Interaction	Management guidelines / monitoring parameters
1.	**Aspirin + Furosemide**	199	6.5 %	Not specified	pd	Antagonism	Risk of renal toxicity increased with combinations NSAID and diuretics, natriuretic effect of diuretics decreased in some patients / monitor for signs of worsen renal function and assure diuretic efficacy
2.	**Aspirin + Clopidogrel**	197	6.4 %	Not specified	pd	Additive	May increase risk of bleeding /monitoring of blood count may be warranted
3.	**Clopidogrel + Esomeprazole**	174	5.6 %	Rapid	pk	Metabolism	↓ level of clopidogrel metabolites & ↓ antiplatelet activity / consider alternative H2 antagonists Ranitidine, platelet aggregation not significantly alerted by h2 antagonists
4.	**Aspirin + Spironolactone**	152	4.9 %	Not specified	pd	Antagonism	Concomitant use NSAID and diuretics ↑K, ↓diuretic and antihypertensive effect. /monitor for renal function, blood pressure and serum K
5.	**Metoclopramide + Tramadol**	111	3.6 %	Not specified	pd	Additive	↑ risk of CNS depression / monitor for adverse effect is necessary

6.	**Aspirin + Heparin**	102	3.3 %	Not specified	pd	Additive	↑ risk of bleeding / evaluate any sign or symptoms of blood loose
7.	**Clopidogrel +Heparin**	102	3.3 %	Not specified	pd	Additive	↑ risk of bleeding / evaluate any sign or symptoms of blood loose
8.	**Clopidogrel + Enoxaparin**	93	3 %	Not specified	pd	Additive	↑ risk of bleeding / evaluate any sign or symptoms of bleeding lab monitoring may be appropriate
9.	**Clopidogrel + Tramadol**	88	2.9 %	Rapid	pk	Metabolism	↓ clopidogrel efficacy /consider the use of parental antiplatelet
10.	**Aspirin + Enoxaparin**	66	2.1 %	Not specified	pd	Additive	↑ risk of bleeding / evaluate any sign or symptoms of blood loose

Table 4 reports top ten most repeated drug –drug ınteraction pairs of major ınteraction. The (Aspirin + Furosemide) and (Aspirin + Clopidogrel) Pairs were the highest first and second Drug-drug Interaction Pairs (199, 6.5%) and (197, 6.4%) which were prescribed for patients. After that, the (Clopidogrel + Esomeprazole), and (Aspirin + Spironolactone) Drug-drug Interaction Pairs were nearly same that were (174, 5.6%) and (152, 4.9%) respectively. Finally, the (Aspirin + Enoxaparin) was the lowest Drug-drug Interaction Pairs that was (66, 2.1 %). Regarding of type of onset, documentation of ınteraction and type of ınteraction, out of top ten, two third of them were not specified onset, and pharmacodynamics interaction respectively.

Table 5:Identified Top Ten of Most Repeated Moderate Interaction Pairs.

NO.	Drug-Drug Interaction Pairs	Frequency	%	Type of onset	Type of Interaction	Mechanism of Interaction	Management guidelines / monitoring parameters
1.	**Aspirin + Bisoprolol**	166	5.4 %	Delayed	pd	Antagonism	NSAIDs ↓antihypertensive efficacy of beta blockers /monitor blood pressure required
2.	**Acetaminophen + Warfarin**	84	2.7 %	Delayed	pk	Metabolism	↑ risk of bleeding at moderate to high dose INR monitoring required frequently for several weeks
3.	**Esomeprazole + Warfarin**	81	2.6 %	Not specified	Unknown	Unknown	↑ INR values and potentiate anticoagulant effect /monitoring prothrombin and INR required
4.	**Heparin + Warfarin**	69	2.2 %	Not specified	pd	Additive	↑ risk of bleeding / more frequent monitoring for PT&INR is required
5.	**Spironolactone + Warfarin**	64	2.1 %	Delayed	pd	Additive	↓ anticoagulant activity / PT or INR should be monitored and adjustment of the warfarin dose may be necessary in

							order to maintain the desired level of anticoagulant
6.	**Aspirin + Insulin**	59	1.9 %	Not specified	Unknown	Unknown	↑ risk of hypoglycemia / monitor glucose level more frequently and insulin dose adjustment
7.	**Ceftriaxone + Warfarin**	56	1.8 %	Not specified	Unknown	Unknown	↑ risk of bleeding/ INR monitoring more frequently or changing doses of antibiotics even if treatment duration is short term
8.	**Furosemide + Insulin**	52	1.7 %	Not specified	pd	Antagonism	↑ risk of hyperglycemia ,increased insulin requirement /monitor glucose levels more frequently including upon withdrawal of the diuretic
9.	**Bisoprolol + Insulin**	42	1.4 %	Delayed	pk	Metabolism	↓ symptoms of hypoglycemia / monitoring or adjustment dose of antidiabetic agent required
10.	**Candesartan + Spironolactone**	32	1 %	Not specified	pd	Additive	↑ risk of hyperkalemia / serum potassium level monitoring require

Table 5 demostrate top ten most repeated drug –drug ınteraction pairs of moderate ınteraction. The (Acetaminophen + Warfarin) and (Esomeprazole + Warfarin) pairs were almost same and the highest second drug-drug ınteraction pairs (84, 2.7%) and (81, 2.6%) of moderate ınteraction. Finally, the (Candesartan + Spironolactone) drug-drug ınteraction pair was the lowest (32, 1 %). With regard to type of onset, and type of ınteraction, out of top ten, almost five of them were not specified onset, and pharmacodynamics interaction respectively.

Table 6: Identified Top nine of Most Repeated Minor Interaction Pairs.

No.	Drug-Drug Interaction Pairs	Frequency	%	Type of onset	Type of Interaction	Mechanism of Interaction	Management guidelines / monitoring parameters
11.	**Theophylline + Furosemide**	104	3.4 %	Rapid	Unknown	Unknown	Alerted theophylline concentration /theophylline serum concentration should be closely monitored when furosemide added
12.	**Aspirin + Hydrocortisone**	14	0.5 %	Delayed	pd	Additive	↑ risk of gastrointestinal ulceration and sub therapeutic aspirin serum concentration / monitor patients for excessive GIT side effects and for decreased aspirin effectiveness
13.	**Levothyroxine + Warfarin**	8	0.3 %	Delayed	pk	Metabolism	↑ risk of bleeding / PT and INR need to be monitored
14.	**Furosemide + Hydrazine**	1	0.03 %	Rapid	pk	Elimination	Hydralazine causes a significant increase in the plasma clearance of furosemide/serum electrolytes and

							creatinine clearance monitoring required and dose adjustment if needed
15.	**Theophylline + Ranitidine**	2	0.1 %	Delayed	pk	Metabolism	↑theophylline toxicity (nausea, vomiting palpitation, seizure)/ theophylline concentrations should be closely monitored
16.	**Aspirin + Ranitidine**	1	0.03 %	Not specified	pk	Absorption	↓ salicylate plasma levels and ↓ antiplatelet effect of aspirin /these combinations should be taken with caution
17.	**Bisacodyl + Cimetidine**	1	0.03 %	Rapid	Unknown	Unknown	↓ in bisacodyl effectiveness / not taking bisacodyl within one hour of taking an H2 blocker
18.	**Ranitidine + bisacodyl**	1	0.03 %	Rapid	Unknown	Unknown	↓ in bisacodyl effectiveness / not taking bisacodyl within one hour of taking an H2 blocker
19.	**Diltiazem + Ranitidine**	1	0.03 %	Delayed	pk	Metabolism	↑ diltiazem concentration and possible cardiovascular toxicity / blood pressure and heart rate monitoring required / famotidine may be alternative H2 antagonist

Table 6 demonstrates top ten most repeated drug –drug ınteraction pairs of minor ınteraction. The (Theophylline + Furosemide) pair was the highest and first drug-drug ınteraction pair (104, 3.4%) which were prescribed for patients. After that, the (Aspirin + Hydrocortisone) was the second drug-drug ınteraction pair that was (14, 0.5%). Nearly, half of drug –drug ınteraction pairs of minor ınteraction were (1, 0.03 %) respectively.

In terms of type of ınteraction and mechanism of interaction, out of top ten, half of them were pharmacokinetics and metabolism ınteraction respectively. Regarding type of onset ınteraction three of them were rapid, delayed and not specified onset.

Table 7: Severity of Identified Most Repeated Drug Interaction Pairs with Lexi Comp Drug Interaction Checker

No.	Drug-Drug Interaction Pairs	Frequency	Mechanisms of interaction	Severity	Interaction Levels	Clinical Significance	Recommendation
1.	**Aspirin + Furosemide**	199	PK	Moderate	C	Aspirin ↓ The Diuretic Effect of Furosemide	Monitoring Diuretic Response
2.	**Aspirin + Clopidogrel**	197	PD	Moderate	C	Enhance The Antiplatelet Effect	Monitoring Diligence For Signs And Symptoms Of Bleeding
3.	**Clopidogrel + Esomeprazole**	174	PK	Major	X	Esomeprazole ↓ Effect of Clopidogrel	Rabeprazole or Pantoprazole may be Lower-Risk Alternatives to Esomeprazole.

4.	**Aspirin + Spironolactone**	152	PD	Minor	C	Aspirin may ↓h the therapeutic effect of Spironolactone	Monitor for ↓spironolactone efficacy. Spironolactone dose ↑ may be needed.
5.	**Metoclopramide + Tramadol**	111	PD	Moderate	C	Metoclopramide may enhance the CNS depressant effect of tramadol	Monitor patients for increased CNS depressant effects
6.	**Aspirin + Heparin**	102	PD	Moderate	D	Aspirin enhance the anticoagulant effect of heparin	↓the dose of heparin or agents with antiplatelet properties
7.	**Clopidogrel + Heparin**	102	PD	Moderate	D	Clopidogrel enhance the anticoagulant effect of heparin	↓ the dose of heparin or agents with antiplatelet properties
8.	**Clopidogrel + Enoxaparin**	93	PD	Moderate	D	may enhance the anticoagulant effect of Enoxaparin	Discontinue antiplatelet agents prior to initiating enoxaparin or monitor closely for signs and symptoms of bleeding.
9.	**Aspirin + Enoxaparin**	66	PD	Moderate	D	Aspirin may enhance the anticoagulant effect of Enoxaparin	Discontinue antiplatelet agents prior to initiating enoxaparin or monitor closely for signs and symptoms of bleeding.

10.	**Acetaminophen + Warfarin**	84	Unknown	Moderate	C	Acetaminophen May Enhance the Anticoagulant Effect of warfarin	Monitor for increased therapeutic effects of anticoagulants
11.	**Esomeprazole + Warfarin**	81	PK	Moderate	C	Esomeprazole may ↑ the serum concentration of Vitamin K Antagonists	monitor for ↑anticoagulant response (ie, increased INR and / or signs and symptoms of bleeding).
12.	**Heparin + Warfarin**	69	PD	Moderate	C	Anticoagulants May Enhance the Anticoagulant Effect of Vitamin K Antagonists	short-term co-administration of a vitamin K antagonist with a non-vitamin K antagonist anticoagulant is a common strategy
13.	**Spironolactone + Warfarin**	64	PD	Moderate	B	Potassium-Sparing Diuretics may diminish the anticoagulant effect of Vitamin K Antagonists	No action needed
14.	**Aspirin + Insulin**	59	Unknown	Moderate	C	Salicylates may enhance the hypoglycemic effect of Agents with Blood Glucose Lowering Effects	Monitor for excessive pharmacological effect (eg, hypoglycemia)

15.	**Ceftriaxone + Warfarin**	56	Unknown	Moderate	C	Cephalosporin's May Enhance the Anticoagulant Effect of Vitamin K Antagonists.	Monitor for elevated INR and bleeding
16.	**Furosemide + Insulin**	52	Unknown	Moderate	C	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic	Monitor blood glucose more frequently
17.	**Bisoprolol + Insulin**	42	PK	Moderate	C	beta blockers may enhance the hypoglycemic effect of insulins.	Monitor for ↑therapeutic effects of insulin
18.	**Candesartan + Spironolactone**	32	Unknown	Major	C	Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics	Monitor for increased risk of hyperkalemia
19.	**Aspirin + Hydrocortisone**	14	Unknown	Moderate	C	Salicylates may enhance the adverse / toxic effect of corticosteroids	Monitor for decreased therapeutic effects of salicylates and GI ulceration
20.	**Levothyroxine + Warfarin**	8	Unknown	Moderate	C	Thyroid Products may enhance the anticoagulant effect of Vitamin K	Monitor for increased anticoagulant effects of vitamin K antagonists

Table 7 demostrate the severity of ıdentified most repeated drug ınteraction pairs with lexi comp drug ınteraction checker. Of 29 identified most repeated drug interaction pairs in Micromedex 10 of them was major in severity ,10 moderate in severity and 9, minor in severity. In contrast of 29 identified pair 9 of them was absent in Lexicomp and 2 of them was major in severity ,17 of them moderate in severity and 1 of them was minor in severity. Regarding level of interaction 14 of them was C ,4 of them was D and 1 of them was X.

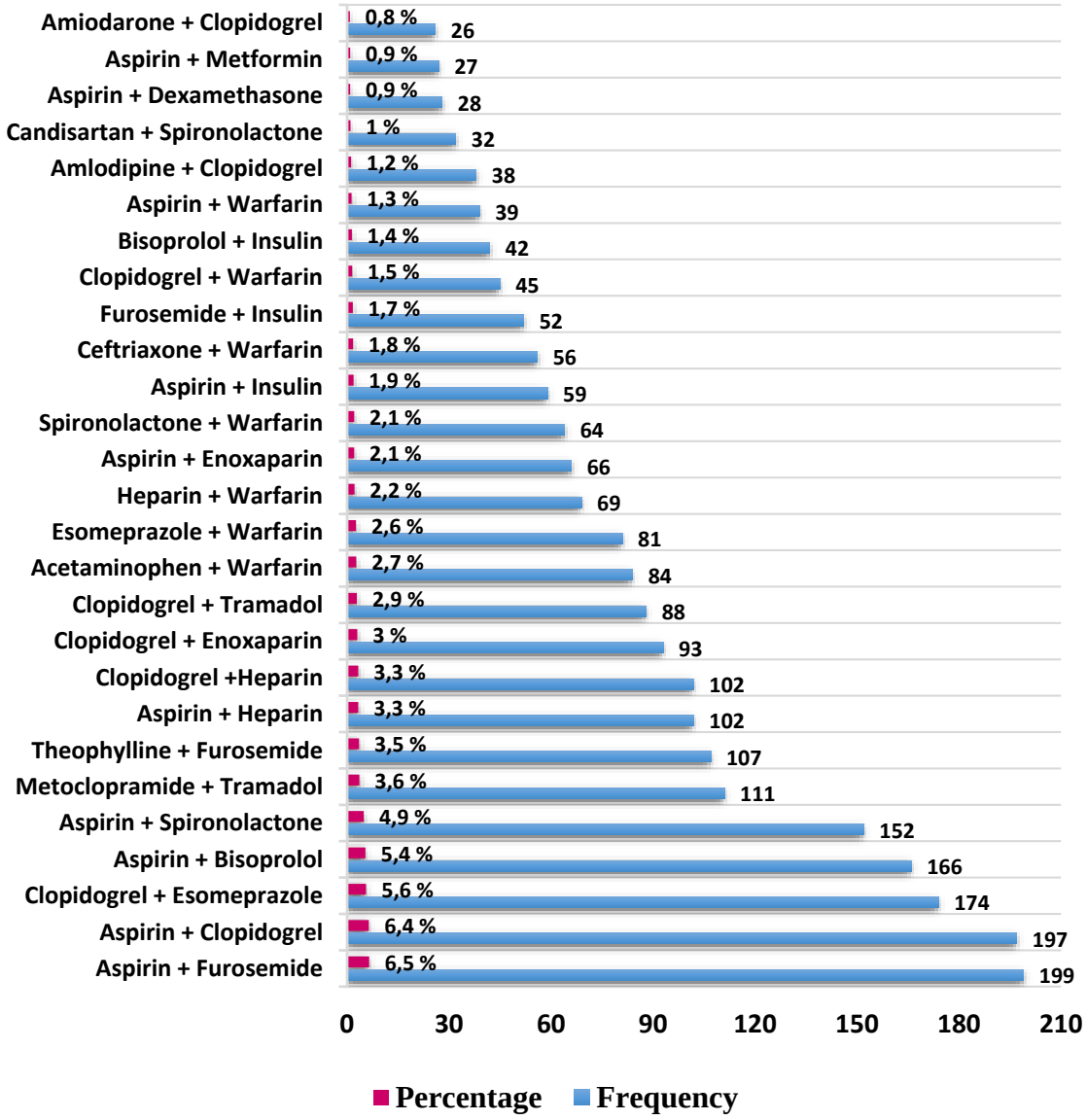

Figure 7: Frequency of Most Repeated Drug-drug Interaction Pairs.

The Figure 7 shows that the frequency of most repeated drug-drug ınteraction pairs. The (Aspirin + Furosemide) and (Aspirin + Clopidogrel) pairs were the highest first and second drug-drug ınteraction pairs (199, 6.5%) and (197, 6.4%) which were prescribed for patients. After that, the (Clopidogrel + Esomeprazole), (Aspirin + Bisoprolol) and (Aspirin + Spironolactone) drug-drug ınteraction pairs were nearly same that were ((174, 5.6%) (166, 5.4%) and (152, 4.9%) respectively. Finally, the (Aspirin + Dexamethasone), (Aspirin + Metformin) and (Amiodarone + Clopidogrel) were nearly same and the lowest drug-drug ınteraction pairs that were (28, 0.9%) (27, 0.9%) and (26, 0.8%) respectively.

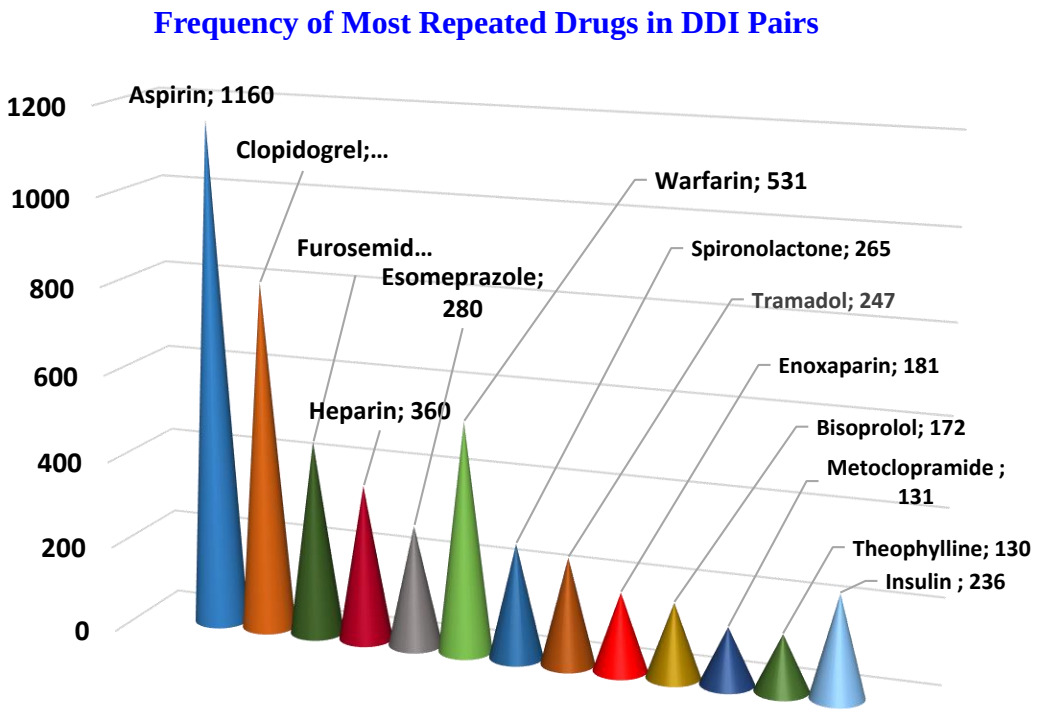

Figure 8: Frequency of Most Repeated Drugs in DDI Pairs.

The Figure 8 reveals that drugs the frequency of most repeated in drug-drug ınteraction pairs. The aspirin was the highest frequent drug (1160) times that was interacted with other drugs which were prescribed for patients. After that, the Clopidogrel and Warfarin were the second and third highest drugs that were (805) (531) times that were interacted with other drugs respectively. In Addition to that, the Tramadol and Insulin type were more or less the same which were (247) and (236) respectively. Finally,

the Metoclopramide and Theophylline were the lowest among top most eleven frequent drugs of drug-drug ınteractions that were (131) and (130) respectively.

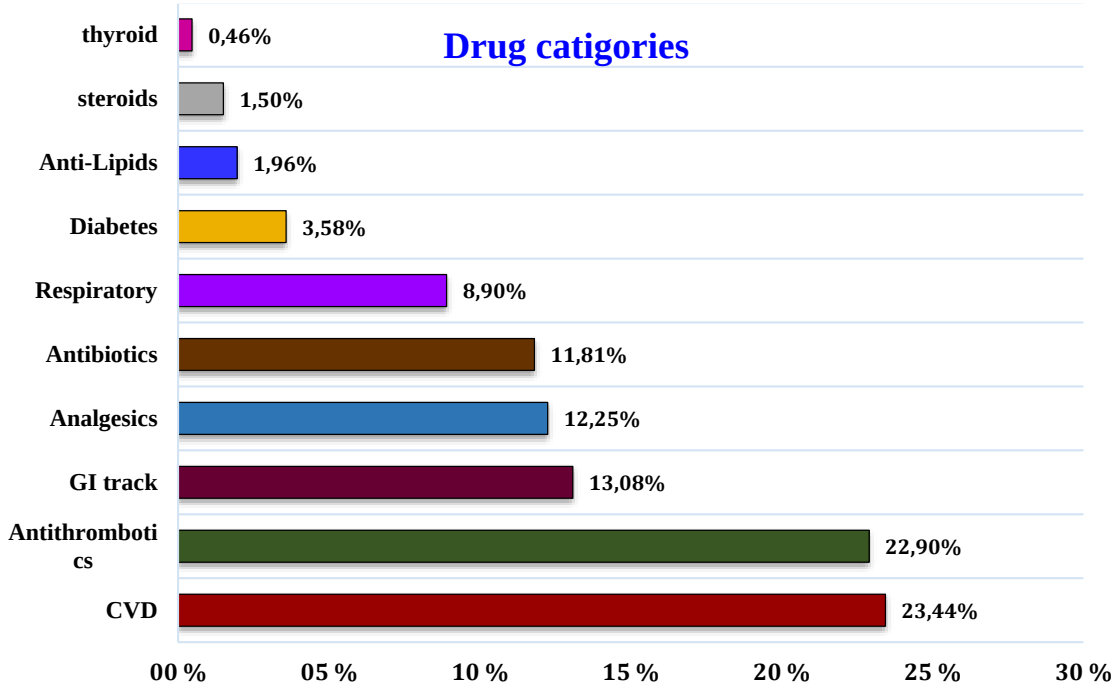

Figure 9: Drug Categories of Drug-drug Interaction Pairs.

In the Figure 9 presents that the drug categories of drug- drug ınteraction pairs. The two highest percentages and nearly same were Cardiovascular Diseases(CVD) and antithrombotic drug categories that were (23.44 %) and (22.9%) respectively. In Addition to that, the GI Track, Analgesic and Antibiotics were had more or less the same percentage which were (13.08 %), (12.25%) and (11.81 %) respectively. Lastly, the steroids and thyroid were the lowest which were (1.5 %) and (0.46 %) respectively.

4.4 Comparison between Demographical data and Numbers of Drug-drug Interaction Pairs:

Table 8: Comparison between Age Groups and Numbers of Drug-drug Interaction Pairs.

		Numbers of Drug-drug Interaction Pairs						
Items		**N**	**%**	**Median**	**Mean Rank**	**df**	**H (Chi-square test)**	**P**
Age Groups of Patients	**19 - 35 years old**	20	6.7 %	6.5	90.70	2	10.584	0.005
	36 - 55 years old	103	34.3 %	9	150.80			
	≥ 56 years old	177	59 %	9	157.08			

Table 8 reveals the comparison between age groups and the number of drug –drug ınteraction pairs. That Kruskal-Wallis Test is used to determine the comparison of age groups indicates that there is a statistically significant differences in the distribution the number of drug –drug interaction pairs between the age groups, the comparison among age groups, there was the mean rank of ≥ 56 years old (157.08) (median= 9) were higher than the mean rank (150.8) of 36 - 55 years old (median= 9) and the mean rank (90.7) of 19 - 35 years old (median= 6.5). The Kruskal-Wallis test indicated that there was a statistically significant differences in the distribution the number of drug –drug interaction pairs among the age groups, h (2) = 10.584, p value =0.005. that is because the p value was less than 0.05.

Table 9: Comparison between Gender and Numbers of Drug-drug Interaction Pairs

		Numbers of Drug-drug Interaction Pairs						
Items		**N**	**%**	**Median**	**Mean Rank**	**U Test**	**Z score**	**P**
Gender of Patients	**Male**	219	73 %	9	148.14	8353.5	- 0.776	0.438
	Female	81	27 %	10	156.87			

Table 9 illustrates comparison between gender and numbers of drug-drug ınteraction pairs. The Mann-Whitney U test is used to compare whether there is a difference in the drug –drug ınteraction pairs among gender of patients. The comparison among male and female, there was the mean rank (156.87) of female (median= 10) were higher than the mean rank (148.14) of male (median= 9), a Mann-Whitney test indicated that there was not a statistically significant differences in the distribution the number of drug –drug interaction pairs between male and female, U (N Male=219, N Female= 81) =8353.5, Z= - 0.776, P < 0.438. That is because the p value was more than 0.05.

4.5 Comparison between Clinical Information Variables and Numbers Drug-drug interactions Pairs:

Table 10: Comparison between Clinical Information Variables and Numbers of Drug-drug Interaction Pairs

		Numbers of Drug-drug Interaction Pairs						
Items		**N**	**%**	**Median**	**Mean Rank**	**U Test**	**Z score**	**P**
Groups of Hospital Stay	**< 7 days**	118	39.3 %	9	138.19	9285.5	-1.985	0.047
	≥ 7 days	182	60.7 %	10	158.48			
Comorbidities								
Diabetic Mellitus	**No**	197	65.7 %	9	131.72	6445.5	-5.201	0.000
	Yes	103	34.3 %	12	186.42			
Hypertension	**No**	21	7 %	5	69.74	1233.5	-4.436	0.000
	Yes	279	93 %	10	156.58			
Dyslipidemia	**No**	155	51.7 %	9	139.94	9600	-2.187	0.029
	Yes	145	48.3 %	10	161.79			
Respiratory Disease	**No**	262	87.3 %	9	146.86	4024	-1.914	0.056
	Yes	38	12.7 %	10	175.61			
Thyroid Disease	**No**	280	93.3 %	9	147.63	1996	-2.151	0.031
	Yes	20	6.7 %	13	190.70			

Table 10 presents comparison between clinical ınformation variables and drug-drug interactions pairs. The Mann-Whitney U test is used to compare whether there is a difference in the drug –drug ınteraction pairs among clinical ınformation variables. The comparison among groups of hospital stay, there was the mean rank (158.48) of ≥ 7 days (median= 10) were higher than the mean rank (138.19) of < 7 days (median= 9), a Mann-Whitney test indicated that there was a statistically significant differences in the distribution the number of Drug –drug interaction Pairs between < 7 days and ≥ 7 days Groups, U (N ≥ 7 days =182, N < 7 days = 118) =9285.5, Z = -1.985, P < 0.047. That is because the p value was less than 0.05.

Apart from that, The comparison among types of comorbidities. Regarding Diabetic Mellitus, there was the Mean Rank (186.42) of those whom have Diabetic Mellitus (Median= 12) were higher than the Mean Rank (131.72) of those whom have Diabetic Mellitus (Median= 9), a Mann-Whitney test indicated that there was a statistically significant differences in the distribution the number of Drug –drug interaction Pairs between those have and Don`t have Diabetic Mellitus, U (N have Diabetic Mellitus =103, N Don`t have Diabetic Mellitus = 197) = 6445.5, Z = -5.201, P < 0.000. That is because the p value was less than 0.05.

Additionally, as regards Hypertension, there was the Mean Rank (156.58) of those whom have Hypertension (Median= 10) were higher than the Mean Rank (69.74) of those whom don`t have Hypertension (Median= 5), a Mann-Whitney test indicated that there was a statistically significant differences in the distribution the number of Drug –drug interaction Pairs between those have and Don`t have Hypertension, U (N have Hypertension =279, N Don`t have Hypertension = 21) = 1233.5, Z = -4.436, P < 0.000. That is because the p value was less than 0.05.

Furthermore, about Dyslipidemia, there was the Mean Rank (161.79) of those whom have Dyslipidemia (Median= 10) were higher than the Mean Rank (139.94) of those whom don`t have Dyslipidemia (Median= 9), a Mann-Whitney test indicated that there was a statistically significant differences in the distribution the number of Drug –drug interaction Pairs between those have and don`t have Dyslipidemia, U (N have

Dyslipidemia =145, N Don`t have Dyslipidemia = 155) = 9600, Z = -2.187, P < 0.029. That is because the p value was less than 0.05.

Likewise, concerning Respiratory Disease , there was the Mean Rank (175.61) of those whom have Respiratory Disease (Median= 10) were higher than the Mean Rank (146.86) of those whom don`t have Respiratory Disease (Median= 9), a Mann-Whitney test indicated that there was not a statistically significant differences in the distribution the number of Drug –drug interaction Pairs between those have and don`t have Respiratory Disease, U (N have Respiratory Disease = 38, N Don`t have Respiratory Disease = 262) = 4024, Z = -1.914, P < 0.056. That is because the p value was more than 0.05. Last of all, as to Thyroid Disease , there was the Mean Rank (190.70) of those whom have Thyroid Disease (Median= 13) were higher than the Mean Rank (147.63) of those whom don`t have Thyroid Disease (Median= 9), a Mann-Whitney test indicated that there was a statistically significant differences in the distribution the number of Drug –drug interaction Pairs between those have and don`t have Thyroid Disease, U (N have Thyroid Disease = 20, N Don`t have Thyroid Disease = 280) = 1996, Z = -2.151, P < 0.031. That is because the p value was less than 0.05.

4.6 Comparison between Groups of Prescribed Medication and Numbers of Drug-drug Interaction Pairs

Table 11: Comparison between Groups of Prescribed Medication and Numbers of Drug-drug Interaction Pairs

		Numbers of Drug-drug Interaction Pairs						
Items		**N**	**%**	**Median**	**Mean Rank**	**df**	**H (Chi-square test)**	**P**
Groups of Prescribed Medication	**< 7 Drugs**	15	5 %	2	23.70	2	75.673	0.000
	8 - 14 Drugs	213	71 %	9	137.92	9		
	≥ 15 Drugs	72	24 %	13	214.12	13		

Table 11 shows that the comparison between groups of prescribed medication and the number of drug –drug ınteraction pairs. That Kruskal-Wallis Test is used to find the comparison of Groups of Prescribed Medication indicates that there is a statistically significant differences in the distribution the number of Drug –drug interaction Pairs between the Groups of Prescribed Medication. The Comparison among the Groups of Prescribed Medication, there was the Mean Rank (214.12) of ≥15 Drugs (Median= 13) were higher than the Mean Rank (137.92) of 8 - 14 Drugs (Median= 9) and the Mean Rank (23.7) of ≤ 7 Drugs (Median= 2). The Kruskal-Wallis Test indicated that there was a statistically significant differences in the distribution the number of Drug –drug interaction Pairs among the Groups of Prescribed Medication, H (2) = 75.673, p value =0.000. That is because the p value was less than 0.05.

4.7 The Comparison between Stockley and two other Software Drug Checkers for evaluating the most Frequent pairs of DDI Regarding Accuracy

Table 12: The Comparison between Stockley and two other software Programs for evaluating the most Frequent pairs of DDI Regarding Accuracy

Programs	TP	FN	TN	FP	Sensitivity	Specificity	PPV	NPV	Accuracy	P value
Micromedex®	15	1	0	5	0.75	0	0.94	0	169	> 0.5
Lexicomp	14	1	0	1	0.93	0	0.93	0	186	

Table 12 reveals the comparison between Stockley and two other Software Programs for evaluating the most Frequent pairs of DDI Regarding Accuracy. The Lexicomp program was more accurate than Micromedex®. That were 186 and 169 out of 400 respectively. Chi-square test revealed that the differences of accuracy scores between programs were statistically not significant ($P > 0.05$). That is probably because the number of most frequent DDI were not all present in all software programs of DDI Checkers. The percentage of correct answers (TN plus TP) were almost the same of both programs (15 and 14 out of 29, 51.7% and 48.3%). The percentage of incorrect answers (FP plus FN) was higher in Micromedex® than in Lexicomp (6 and 2 out of 29, 63.3%), respectively. In terms of Specificity was the same in Micromedex® and Lexicomp programs (0) and the Sensitivity was (0.75 and 0.93) respectively.

CHAPTER V

Discussion

DIs are a significant clinical concern in healthcare, particularly for critically ill patients. Evaluating potential DDIs not only reveals prescription errors, but also helps with medical care by informing medical teams of the precautions to take when administering specific drugs. Polypharmacy, co-morbidities, hospitalization period of and patient's state of health are factors that contribute to the development of DDI which could lead to adverse drug effects, prolonged hospitalization , increased health care costs and reduced quality of life for patients (Khan et al., 2017).

In our research, CTS patients had clinical characteristics that put them in a high-risk group for DDIs, such as Nearly two third of the participants were above 56 years' old, admission for CTS (primarily for CABG surgery), comorbidities (average of five), a high number of prescribed medications median 12 (3). Drugs drugs), and 39.3% of them being hospitalized for more than 7 days (Janković et al., 2018 ; Murtaza, 2015).

Most of the patients admitted to the hospital for CTS surgeries had at least one potential DDI during their stay, and the prevalence of pDDIs was 97.3 % in our study. A comparable study was conducted a few years ago in the Department of Cardiology of the Ayub Teaching Hospital (ATH), Abbottabad for the period one year they found The prevalence of pDDI to be 91.6 % among randomly selected cardiac patients (Murtaza, 2015).

According to a study conducted in six different hospitals in Jordan, the prevalence of pDDIs in cardiology and internal medicine outpatient clinics was 96.0 %. (Nusair et al., 2020). for there more A six-month study of DDI at a teaching hospital in South India found that DDI was responsible for 91% of the 204 total prescriptions (Kulkarni et al., 2013). In contrast Mousavi and Ghanbari (2017) found that 86.2 % of hospitalized patients had probable DDIs using the Lexi-comp and Micromedex Drug-Reax systems. Another study of cardiac patients at an Iranian hospital found a 43.4 % prevalence rate for pDDIs. (Namazi & Moosavi, 2012).

The higher prevalence of pDDIs in our study could be attributed to the inclusion of all grades of pDDIs; approximately two-third of our study populations were above 56

year old , and we followed the admitted cardiac patients throughout their hospital stay, which may increase drug interaction risks from multiple-drug exposure in inpatients. A few other studies imply that cardiac patients are at a higher risk of pDDIs since a number of cardiac medicines are linked to pDDIs, and these patients are more prone to pDDIs due to disease complexity and poly pharmacy drug therapy (Albadr et al., 2014 ; Smithburger et al., 2010 ; Straubhaar et al., 2006).

In accordance with the mechanisms investigated in this study, DDIs were classified as pharmacodynamics, pharmacokinetic, or unknown by Micromedex. The pharmacodynamics and pharmacokinetic mechanisms were responsible for the majority of DDIs reported in our study. Pharmacodynamics interactions were responsible for (65.4 %) of the DDIs, while pharmacokinetic interactions were responsible for (21%), and unknown (13.6%). Similarly, a recent study in 2018 found that pharmacodynamics interactions (53.27 %) were the most common cause of DDIs in hospitalized patients in cardiac and pulmonary departments, while pharmacokinetic interactions (29.90 %) and unknown (8.54 %) causes were less common (Ramalingam et al., 2018).

Another study, performed by Chavda et al., found that 50.83 % of DDIs are pharmacodynamics interactions, whereas 38.53 % are pharmacokinetic interactions (Chavda et al., 2015). However, these findings contrast from those of another study, which found that among the 856 interactions, pharmacokinetic DDIs (42 %) were more prevalent than pharmacodynamics DDIs (24 %) and unknown mechanisms (34 %) (Kulkarni et al., 2013).This distinction could be attributed to differences in the disease characteristics of the patients, resulting in a variation in the type of medications given.

The severity assessment in our study revealed that most of these interactions were classified as major interactions (59.3%), followed by moderate (36.2%), and minor (4.5%) this is higher than the percentage reported in a study conducted in surgical ward in three Palestinian and Mexican hospitals which was (56%) and (49.5%) (Rabba et al., 2020 ; Sánchez-López et al., 2016). This difference could be related to differences in the methodologies used to identify and classify pDDIs. These possible DDIs point to the necessity for therapeutic modification or alteration, such as dosage adjustments. To avoid these DDIs, healthcare providers must have sufficient information about DDIs, not only through drug information centers that can provide evidence-based information to health-

care professionals, but also by empowering clinical pharmacists to provide an evidence-based approach to drugs and thus prevent drug therapy problems, of which DDIs is one.

Micromedex reported very high DDI rate of major in severity in compare to Lexicomp. Our result is similar to a retrospective study conducted in community pharmacy chain in Qatar they reported Micromedex classified 61.6 % of drug interaction pairs as major in severity and Lexicomp classified 30.8% as major in severity (Abbas et al., 2021). Another study conducted in cardiovascular department and its intensive care unit (ICU) of Assiut University Hospitals, Egyp aimed to compare grading of potential drug- drug interaction between three different software they reported that most common potential drug-drug interactions were moderate in severity and those contraindicated were the least, although the major grading in Micromedex® was the largest (Raslan et al., 2018).

Regarding accuracy The study analyzed the sensitivity, specificity, and accuracy of several DDIs screening software and found that Lexi-Interact was the most accurate and had the excellent score (Kheshti et al., 2016). In this study the Researcher compare the Most Frequent DDI Pairs (29 DDI Pairs) in Micromedex® and Lexicomp program with Stockley Program Checker, which the Lexicomp program was more accurate and sensitive were than Micromedex® but it was not statistically significant that was because all 29 DDI Pairs were not present in Lexicomp program and Stockley Program Checker. So, the number of DDI pairs among them, was small.

Our study found some associations with occurrence of pDDIs that involve patients. Age, length of hospital stays, polypharmacy and comorbidities. Other studies have found Significant associations of pDDIs with various factors. Our result regarding association of potential drug-drug interaction with age of patients are supported by other studies as well (Bacic-Vrca et al., 2010).Our study found that older age has association to the occurrence of pDDIs ($p = 0.005$). A study conducted at Palestinian Hospitals on patients admitted to the surgery department also revealed that patients have older age were at a higher risk for pDDIs (Rabba et al., 2020). And also another study conducted at the Department of Cardiology of the Ayub Teaching Hospital they discovered that age as a risk factor for PDDIs (Murtaza et al., 2016). A study conducted in Switzerland on

cardiovascular patients found that patients have older the age were at a higher risk for pDDIs (Egger et al., 2007).

Another study in patients receiving antihypertensive medicines in the Medicaid population observed a strong association between pDDIs and an increase in age (Carter et al., 2002). Another study conducted in the cardiac intensive care units of the two hospitals in Pakistan, found a strong association between pDDIs and an increase in age (Shakeel et al., 2016) Patients' ages are likely to be related with a higher risk of interactions, presumably due to a higher risk of comorbid diseases and receiving higher number of medicine (polypharmacy).

Another association with the occurrence of pDDI reported in our study is a prolonged hospital stay (P= 0.047). According to the findings of a study done at Palestinian Hospitals on patients admitted to the surgery department it has found that Patients who spent more time in the hospital had a significant association with pDDIs (Rabba et al., 2020) Other studies have identified a similar correlation, which supports our results that a prolonged hospital stay may increase the possibility of pDDI incidence (Bajracharya et al., 2018 ; Sharma et al., 2014 ; Murtaza et al., 2016).This could be due to the chance get more new prescription medicines throughout their hospital stay which in turn increase the risk for pDDIs

Patients in our study who were administered multiple medications were at a higher risk of pDDIs (P = 0.00). A study conducted at a Palestinian surgical ward discovered that the incidence of pDDIs increased with the number of medicines administered (Rabba et al., 2020). Another study conducted in India in the department of general medicine found a similar association (Bajracharya et al., 2018) A few additional research have found a similar association between polypharmacy and the occurrence of pDDIs (Chatsisvili et al., 2010 ; Shakeel et al., 2016 ; Murtaza et al., 2016) Comorbidities were showed significant association with occurrence of pDDIs in our study hypertension (P= 0.00). Other studies have identified a similar correlation, which supports our results that incidence of pDDIs in multimorbidity’s patients have significant association, this is because of receiving higher number of medication, having older age and longer hospitalization (Mallet et al., 2007 ; Bajracharya et al., 2018 ; Magro et al., 2012).

In our study, there was no significant relationship between pDDIs and gender. Various studies have revealed varying outcomes in terms of the association of any gender with the risk of pDDIs. A study of ATH cardiac patients identified a significant association of pDDIs with male patients (Ismail et al., 2012). Another study conducted in Brazil, on the other hand, identified a highly significant relationship of pDDIs with female patients (Cruciol-Souza & Thomson, 2006). There are other studies that support our results. According to an Italian study, pDDIs are not linked to any specific gender (Nobili et al., 2009). Our findings indicate that pDDIs are associated to older patients, polypharmacy, comorbidities, and patients who stay in the hospital for longer periods of time. As pDDIs are a significant factor in patient hospitalization, the pharmacist's role in clinical outcomes of multiple adverse events is essential. A clinical pharmacist can contribute significantly to the improvement of pharmacotherapy. A clinical pharmacist can identify factors that could lead to incorrect prescriptions (Azhar et al., 2009; Viktil & Blix, 2008)

Researchers discovered that the medications usually associated with pDDIs include drugs used for CVD such as furosemide, spironolactone, bisoprolol, amlodipine, candesartan; antithrombotic agents such as clopidogrel, heparin, warfarin, enoxaparin; NSAID such as Aspirin, Acetaminophen, xanthan’s such as theophylline; GITs such as esomeprazole, ranitidine, cimetidine; antibiotics such as ceftriaxone. Our findings suggest that these medications should be taken with constant awareness of potential and clinically significant DDIs.

In this study, the most frequent encountered major DDI combination was aspirin + furosemide so risk of renal toxicity increased with combinations NSAID and diuretics, natriuretic effect of diuretics decreased in some patients by the inhibition of renal prostaglandin synthesis so / monitor for signs of worsen renal function and assure diuretic efficacy. Other more common interaction pair was aspirin and clopidogrel which have pDDI this may increase risk of bleeding /monitoring of blood count may be warranted, followed by clopidogrel + esomeprazole in this combination esomeprazole decreases the level of clopidogrel metabolites and lead to decrease in antiplatelet activity / considering alternative H2 antagonists Ranitidine, platelet aggregation which is not significantly alerted by h2 antagonists , aspirin and spironolactone combinations increase risk of hyperkalemia and decreased diuretic effect of spironolactone and also decrease

antihypertensive effect. /monitor for renal function, blood pressure and serum potassium required. as we have found that antithrombotic combinations were responsible for most of major drug interactions and increase risk of bleeding so evaluate any sign or symptoms of bleeding lab monitoring may be appropriate. Clinical Management guidelines and monitoring parameters recommendations for these combinations was based on clinical management of Micromedex software recommendation. This study is the first study that asses the frequency of pDDIs in hospitalized patients underwent cardiac surgery in Kurdistan region of Iraq.

5.1 Strengths and Limitations

This is the First study in Kurdistan region of Iraq, Lexicomp and Micromedex drug interaction checker used to analyze the severity of top identified drug interaction pairs and an appropriate study design and a relatively large sample size used.

There are some limitations to this study. In this study the Researcher compare the Most Frequent DDI Pairs (29 DDI Pairs) in Micromedex® and Lexicomp program with Stockley Program Checker, it was not statistically significant that was because all 29 DDI Pairs were not present in Lexicomp program and Stockley Program Checker. So, the number of DDI pairs among them, was small.

Another limitation, dverse outcome monitoring due to potential drug drug interaction and lack of intervention were a limitation of our study. This study identified PDDIs based on literature and a drug interaction database, and clinical trials can be undertaken in the future to monitor the real clinically significant adverse effects of these PDDIs and their effect on the patient's disease. The files of died patients were not accessible to study this was another limitation Furthermore, because our study was done at a single hospital in Kurdistan region, the findings may not be fully representative of other hospitals. As a result, the data' generalizability is restricted, and future studies with a greater number of patients and institutions are needed.

CHAPTER VI

Conclusion

Drug-drug interactions are common in CTS Surgery patients however, the future probability of occurrence and degree of patient harm require additional supporting evidence. The results of this study revealed that the prevalence of DDIs in this population were found to be high among patients admitted to CTS surgery department. Despite the fact that Micromedex detects more major interactions than Lexicomp. Previous studies have found deficiencies and variation in drug drug interaction programs none of the two medication interaction screening programs assessed were deemed excellent. However, Lexicomp was better than Micromedex. The clinician's judgment is critical in distinguishing between relevant and irrelevant interactions and to make a final clinical decision, an expert specialist is required.

Polypharmacy, age, duration of stay in hospital and comorbidities had significant association to the number of DDIs. amalgamate of medication review guidelines, design and implementation of a computerized DDI alerts tool (Computerized provider order entry in electronic health record (EHR) systems) recommended to avoid ADRs and occurrence of potential drug-drug interaction within the hospital. Pharmacists must be responsible for monitoring drug interactions and advising doctors and patients about any potential problems. Pharmacists can relate unforeseen side effects observed by patients to inconceivable bad effects of their prescription therapy because of their detailed knowledge of medicines.

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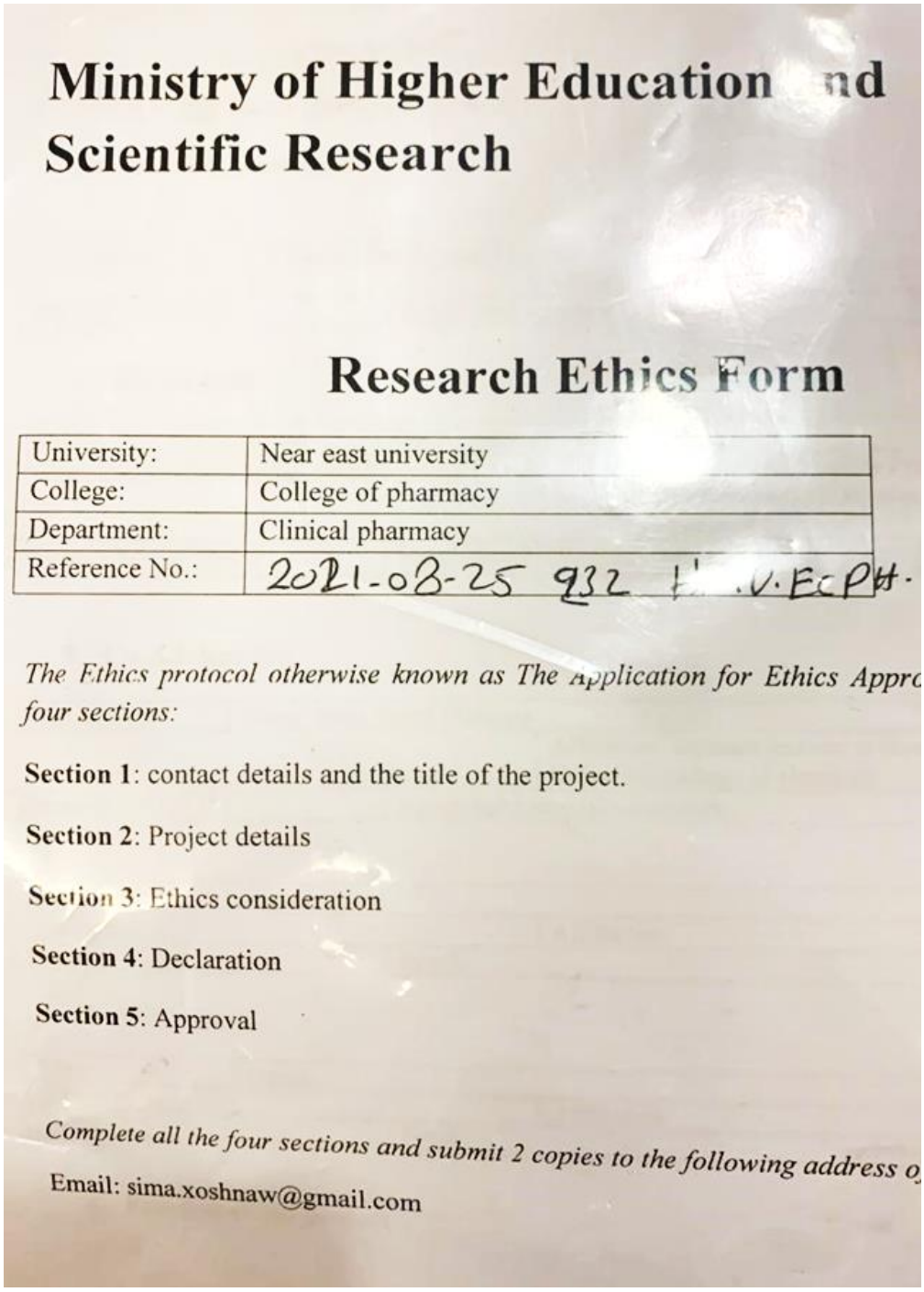
APPENDIXES

Appendix A: Ethical approval



Ministry of Higher Education and Scientific Research

Research Ethics Form

University:	Near east university
College:	College of pharmacy
Department:	Clinical pharmacy
Reference No.:	2021-08-25 932 [illegible]

The Ethics protocol otherwise known as The Application for Ethics Appro four sections:

Section 1: contact details and the title of the project.

Section 2: Project details

Section 3: Ethics consideration

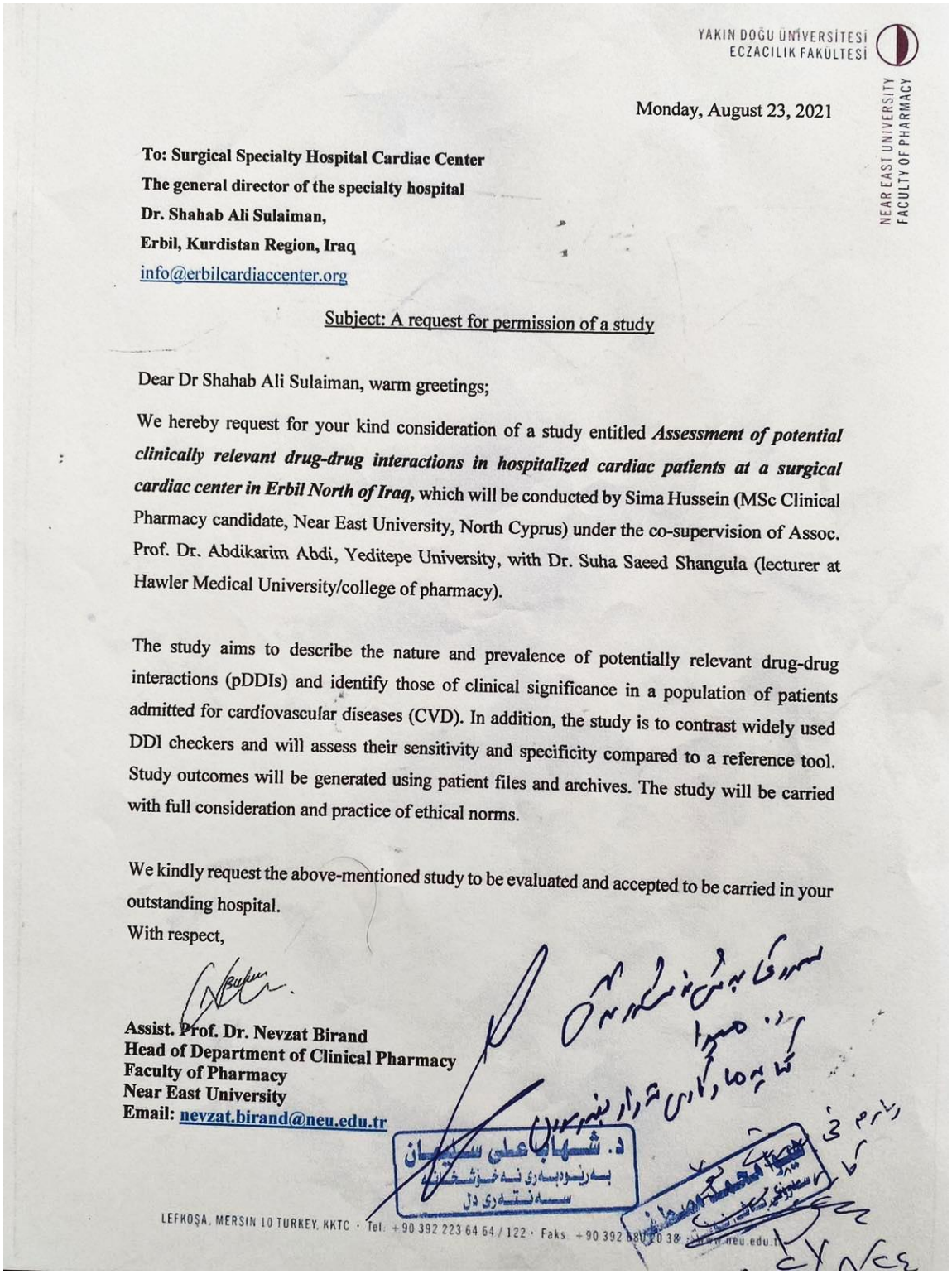
Section 4: Declaration

Section 5: Approval

Complete all the four sections and submit 2 copies to the following address o

Email: sima.xoshnaw@gmail.com

Appendix B : Permission



YAKIN DOĞU ÜNİVERSİTESİ
ECZACILIK FAKÜLTESİ

NEAR EAST UNIVERSITY
FACULTY OF PHARMACY

Monday, August 23, 2021

To: Surgical Specialty Hospital Cardiac Center
The general director of the specialty hospital
Dr. Shahab Ali Sulaiman,
Erbil, Kurdistan Region, Iraq
info@erbilcardiaccenter.org

Subject: A request for permission of a study

Dear Dr Shahab Ali Sulaiman, warm greetings;

We hereby request for your kind consideration of a study entitled ***Assessment of potential clinically relevant drug-drug interactions in hospitalized cardiac patients at a surgical cardiac center in Erbil North of Iraq,*** which will be conducted by Sima Hussein (MSc Clinical Pharmacy candidate, Near East University, North Cyprus) under the co-supervision of Assoc. Prof. Dr. Abdikarim Abdi, Yeditepe University, with Dr. Suha Saeed Shangula (lecturer at Hawler Medical University/college of pharmacy).

The study aims to describe the nature and prevalence of potentially relevant drug-drug interactions (pDDIs) and identify those of clinical significance in a population of patients admitted for cardiovascular diseases (CVD). In addition, the study is to contrast widely used DDI checkers and will assess their sensitivity and specificity compared to a reference tool. Study outcomes will be generated using patient files and archives. The study will be carried with full consideration and practice of ethical norms.

We kindly request the above-mentioned study to be evaluated and accepted to be carried in your outstanding hospital.
With respect,

Assist. Prof. Dr. Nevzat Birand
Head of Department of Clinical Pharmacy
Faculty of Pharmacy
Near East University
Email: nevzat.birand@neu.edu.tr

د. شهاب علی سلیمان
به‌ڕێوبه‌ری نه‌خۆشخانه‌
سه‌نته‌ری دل

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Appendix C : Data collection form

C. Medication History		
Number of Medication	**Generic Name**	**Pharmacological Class**

Patient NO.	Age	Gender	Operation Type	Duration of Stay	Comorbidities	NO. of Prescribed Medicine	NO. DDI

Appendix D : Reasercher`s Curriculum Vitae (CV)

Name	Sima	**Surname**	Hussein
Place of Birth	Iraq	**Date of Birth**	11/10/1993
Nationality	Iraqi	**Tel**	+9647504931060
E-mail	Sima.xoshnaw@gmail.com		

Educational level

	Name of the Institution where he/she was graduated	**Graduation Year**
Postgraduate/Specialization	Near east university	2022
Master	Near East University	2022
Undergraduate	Eastern Mediterranean University	2018
High school	Shaqlawa Typical Preparatory School	2011

Job Experience

Duty	**Institution**	**Duration (Year-year)**
Assistant lecturer	Shaqlawa Technical College	2021
Member of syndicate of Kurdistan pharmacists/Iraq	syndicate of Kurdistan pharmacists/Iraq	2019
Pharmacy director at Darwazay sarban pharmacy-masif-erbil	Darwazay sarban pharmacy-masif-erbil	2020

Foreign Languages	Reading Comprehension	Speaking	Writing
English	Yes	Yes	Yes
Arabic	Yes	Yes	Yes

Foreign Languages Examination

YDS	ÜDS	IELTS	TOEFL IBT	TOEFL PBT	TOEFL CBT	FCE	CAE	CPE
No	No	No	No	No	No	No	No	No

	Math	Equally weigh	Non –math
ALES Grade	No	No	No
(other) Grade	No	No	No

Computer Knowledge

Program	Use proficiency
Microsoft office	Good
Camtasia studio	Good
SPSS	Good

ENCLOSURE: Other.

- Honor certificate 8th semester GPA 3.40
- High honor certificate 9th semester GPA 3.88
- High honor certificate 10th semester GPA 3.81
- Medical seminar attendance four certificates