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NEAR EAST UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

Significant drug-drug interactions in hospitalized patients with chronic diseases at Near East Hospital in Northern Cyprus

A THESIS SUBMITED TO THE GRADUATE INSTITUTE OF HEALTH SCIENCES NEAR EAST UNIVERSITY

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Northern Cyprus, Nicosia

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DEDICATION

This research is dedicated to my father, mother, and sister.

I would never have done this without your faith, support and constant encouragement. Thank you for teaching me to believe in myself and my dreams!

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Approval

Thesis submitted to the Institute of Health Sciences of Near East University in partial fulfillment of the requirements for the degree of **Master of Science in Clinical Pharmacy.**

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ABSTRACT

Drug-drug interactions (DDIs) are an important type of preventable adverse drug events which can lead to patient's hospitalization, adverse drug reaction during hospitalization, re-hospitalizations, or even death. Patients with chronic disease are at high risks to DDI. This study was aimed to assess the frequency of DDIs in patients with chronic diseases during their hospitalization period at Near East University Teaching Hospital in Northern Cyprus.

A cross-sectional retrospective observational was conducted from 01 April to 01 June, 2018. 135 patients with chronic diseases (chronic cardiac diseases, diabetes mellitus, asthma and COPD), who were hospitalized during the study period in cardiology, internal medicine or chest diseases and allergy departments at Near East University Teaching Hospital in Northern Cyprus for one day and more were included. Lexi-Interact tool by Lexi-comp (Wolters Kluwer Clinical Drug Information, Inc.) was used to check the DDIs. Mann-Whitney Test, Chi-square, and One-Way ANOVA were applied to determine the p-values for specific risk factors of DDIs. A p-value of <0.05 was assigned as statistically significant.

Out of 135 patients, 119 patients were found with 840 combinations of possible DDIs. The mechanism of interaction for most of DDIs was pharmacodynamic 60.3%. Most of the DDIs were moderate in severity. Risk rate C has been identified with the greatest number of DDIs 67.8%. Patients had chronic cardiac diseases counted for highest frequency of DDIs 52.3%. There was a significant association of the occurrence of DDIs and the number of administered drugs ($p<0.05$). Drugs prescribed for chronic use have resulted in a significant increase of DDIs ($p<0.05$) compared to drugs for acute use.

We found that hospitalized patients with a chronic disease have a high risk to encounter DDIs during the period of hospitalization. Healthcare providers should be aware of the commonly occurring DDIs. Clinical pharmacists have an important role in the identifying, solving and preventing DDIs.

Keywords: Drug-drug interactions, Chronic diseases, Hospitalization, Cardiology, Internal medicine, Chest diseases and allergy, Hospital pharmaceutical service, Northern Cyprus.

CONTENT

ABBREVIATIONS

ABBREVIATION	EXPLANATION
DRPs	Drug-Related Problems
ADE	Adverse Drug Events
ME	Medication Error
MAEs	Medication Administration Errors
ADR	Adverse Drug Reaction
DDIs	Drug-Drug Interactions
WHO	World Health Organization
ICD 10	Classification of Diseases and Related Health Problems
COPD	Chronic Obstructive Pulmonary Disease
DM	Diabetes Mellitus
CKD	Chronic Renal Failure
CHF	Congestive Heart Failure
CABG	Coronary Artery Bypass Surgery
MI	Myocardial Infarction
HF	Heart Failure
AF	Arterial Fibrillation
AHD	Atherosclerotic heart disease
CVD	Cardiovascular Disease
VTE	Venous Thromboembolism
HVD	Heart Valve Disease
NSAID	Non-Steroidal Anti-Inflammatory Drug
CAD	Coronary Artery Disease

IHD	Ischemic Heart Disease
HIV	Human Immunodeficiency Virus
ACEI	Angiotensin Converting Enzyme Inhibitor
B-blocker	Beta-blocker
B2-agonist	Beta 2-agonist
ADME	Absorption, Distribution, Metabolism, and Excretion
pH	Power of Hydrogen
P-gp	P-glycoprotein
CYP450	Cytochrome P450 Monooxygenase
SPSS	Statistical Package for the Social Sciences
NEU Hospital	Near East University Hospital
ICU	Intensive Care Unit
PK	Pharmacokinetic
PD	Phamacodynamic
GI	Gastrointestinal
PT	Prothrombin Time
INR	International Normalized Ratio
AKI	Acute Kidney Injury
TdP	Torsade de Pointes

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1. INTRODUCTION AND BACKGROUND

1.1. Drug-related problems

1.1.1 Definitions

Therapeutic outcomes are reached when the right drug in the correct dosage and quality delivered to the right patient at the right time point. (Krähenbühl-Melcher, 2007) However, inappropriate drug use may lead to harmful adverse outcomes. (Fijn R, 2002) Since Drug-Related Problems (DRPs) may affect patient's outcomes and result in morbidity or mortality and increased health care costs, it considered as a challenge to the clinician. Clinical pharmacy services include optimizing of drug use by evidence-based guidelines and identifying and resolving of DRPs. (Parthasarati G, 2003)

DRPs became a field of interest when cases of aplastic anemia have been reported after the use of chloramphenicol (Rich ML, 1950) and birth defects following treatment with thalidomide in 1960. (Mellin GW, 1962)

All events or circumstances that actually or potentially impair the desired therapeutic outcomes are defined as Drug-Related Problem (DRPs). (PCNE, 2017) An actual problem leads to clinical manifestations (as drug-related rash, adverse drug reaction) or therapy failure because of incorrect dosage. A potential problem is not apparent and if unresolved it may lead to drug-related harm to the patient. (Viktil, 2008)

DRPs include medication errors (MEs), adverse drug events (ADEs) and adverse drug reactions (ADRs). (Dean BS, 1995) Another division of DRP is intrinsic and extrinsic toxicity. The interaction of the pharmaceutical chemical and/or pharmacological characteristics of the drug itself and the human biosystem is considered as intrinsic toxicity; which is in another word ADRs. (Edwards, 2000) In contrast, the problems caused by inappropriate use of the drug either by the healthcare professional or by the patient are extrinsic toxicity; which is in another word MEs. (NCCMERP, 2006)

In ADR and ADE the patient's harm has occurred as a result of a drug. In more details, an ADR is a harm results from a medication dose that is "normally used in man", while harm associated with any dose of a drug, whether or not the dose is "normally used in man" is ADE. Therefore, ADR is a subtype of an ADE.(NCC MERP, 2015) These terms are defined more precisely in Table 1 and their relationship is illustrated in Figure 1.

Table 1: Definitions of different terms in drug-related problems classification.

Term	Definition
Drug-related problems (DRPs)	All actual or potential problems that experienced by the patient due to the drug treatment that affects the accomplishment of desired treatment outcome. (PCNE, 2017)
Medication error (ME)	An avoidable event that may result in irrational use or patient harm when the drug is actually still used by healthcare providers or patient.
Adverse drug event (ADE)	An unplanned incident that appears during the drug treatment and not always been connected to the treatment. (WHO, Medication Errors: Technical Series on Safer Primary Care, 2016)
Adverse drug reaction (ADR)	A response to a drug that is noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of diseases, or for the modification of physiological functions. (WHO, Medication Errors: Technical Series on Safer Primary Care, 2016)

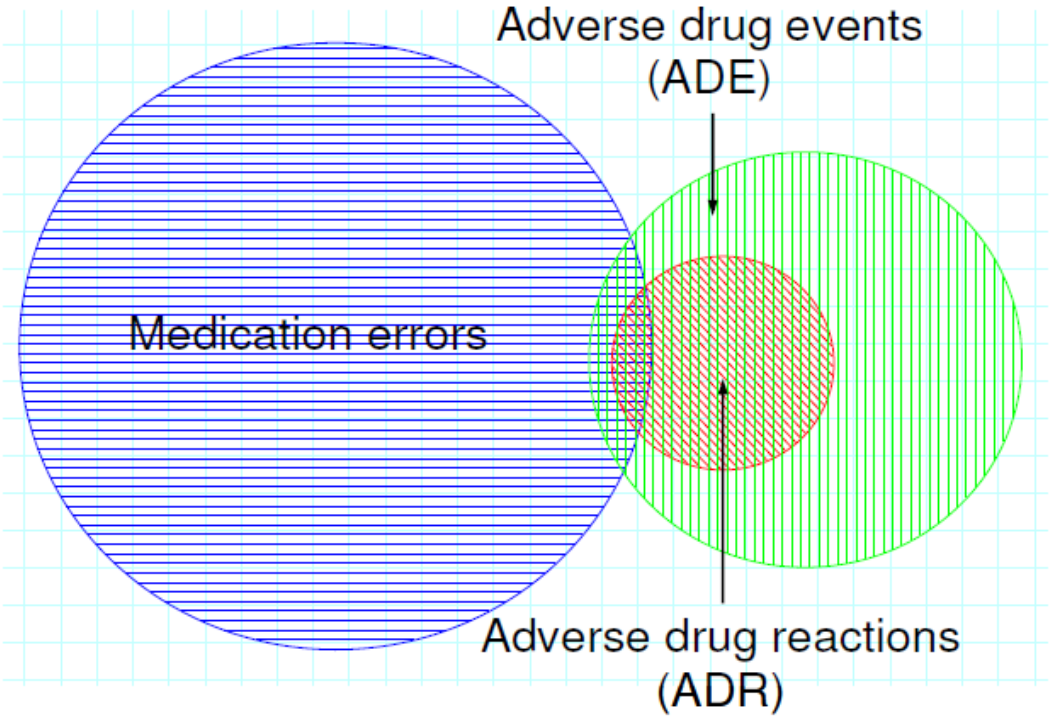

Figure 1: Relationship between medication error (ME), adverse drug event (ADE), and adverse drug reaction (ADR). (Krähenbühl-Melcher, 2007)

1.1.2 Risk factors for drug-related problems

Knowing the risk factors of DRPs is important to develop preventable measures and decrease their incidence.

Polypharmacy, female sex, administration of drugs with a narrow therapeutic index, renal elimination of drugs, age >65 years and the administration of anticoagulants or diuretics are important risk factors for ADEs. (Krähenbühl-Melcher, 2007)

Added to this, more detailed risk factors are considered by Leendertse et al., such as four or more comorbidities, dependent living situation, impaired cognition, impaired renal function and non-adherence to the medication regimen. (Leendertse AJ, 2008)

1.1.3 Classification systems of drug-related problems

The core practice in pharmaceutical care is to detect and resolve the DRPs. Published literatures classify the DRPs in deferent ways due to variations on definitions of DRPs and guidelines. (Meyboom RH, 2000) Also, DRPs classifications are important for documentation which is an essential process in pharmaceutical care. (Currie JD, 2003) Consequently, a validated instrument is needed.

DRPs classifications differ in structures and point of concentration. Some classifications separate the cause of a DRP from the problem itself; while in other classifications the problem describes the cause. Also, other classifications provide a coding system for interventions. The hierarchical structure is used in most modern classifications, where higher levels are broadly defined and lower levels become more specific. New subcategories also can be added in these systems.

Concentrate in some classifications is directed to the patient's perspective and the outcomes of therapy; others are focused on the process of prescribing, dispensing, and drug use. Added to this, other classifications oriented toward research and constructed for pharmacy practice or drug-use evaluation purposes. (Van Mil, 2004)

Validation of DRPs classification instrument is important to ensure that the code used to address a DRP and will be clearly understood. In 2004, Van Mil et al. developed 5 major requirements for validation of DRP classifications; which are:

1. A clear definition for both the DRP in general and for each DRP category.
2. Published validation of the classification instrument.
3. Usable in practice and have been used in a published study.
4. Structured in a hierarchical way with clear groups, subgroups; and an open structure to add new problems.
5. Classification should be on the drug use process and outcome and separate the problem itself from the cause (Van Mil, 2004)

1.1.4 Drug-related problems in hospitalized patients

DRPs are frequent in hospitalized patients and may lead to increase in patient morbidity and mortality, and costs. (Kongkaew, 2008) In addition, previous studies showed that DRPs is the main cause of hospitalization. (Blix, 2004)

A surveillance study of admitted patients to the Department of Internal Medicine in a Swedish university hospital over a 3.5 months period, demonstrated that over 285 patients, 45 patients were admitted due to DRPs. (Bergman, 1981)

In a systematic review of 25 prospective observational studies that used the WHO definition of ADR, 5.3% of hospital admissions were associated with ADRs. Elderly patients found to have highest rates as long as they use multiple medications for long-term illnesses. (Kongkaew, 2008)

Another review of articles published between 1990 and 2005 about drug-related problems in the hospital, revealed that MEs occur in about 5% and that ADEs occur in about 6% of hospitalized patients. (Krähenbühl-Melcher, 2007)

Moreover, Van den Bemt and associate found that the rates of MEs (1.7 to 59%) and ADRs (1.9 to 37.3%) in hospitalized patients are higher than ADEs (0.7 to 6.5%). (Van den Bemt, 2000)

Medication-related hospital admissions can be preventable. A prospective study of frequency of preventable medication-related hospital admissions in the Netherlands showed that 5.6% of 12 793 unplanned admissions were medication related and 46.5% of these admissions were potentially preventable. (Leendertse AJ, 2008)

Added to this, even serious ADEs are more likely to be preventable. A prospective cohort study over 6 months identified 247 ADEs and 194 potential ADEs. Throughout the 247 ADEs, 70 (28%) were preventable, and 83 (43%) of the potential ADEs were detected before the drug was given. (Bates D. W., 1995)

1.2. Medication errors

An important part of DRPs is the medication errors (MEs). (Van den Bemt, 2000) MEs are strong risk factors for preventable ADE or ADR. (Krähenbühl-Melcher, 2007) In fact, MEs are pre-stage of ADRs. (Van den Bemt, 2000) Actually, the majority of ME cases do not result in ADR. (Bond C. A., 2002) Several studies found that not more than 10% of MEs have resulted in ADR (Lazarou J, 1998) while almost 1% of medication errors resulted in an ADE. Moreover, a small part only of MEs represent an ADE or a potential ADE, and all potential ADEs considered as MEs. (Bates D. W., 1995) Despite this, knowledge of MEs origin and of possible risk factors is necessary because they can be avoided. (Bond, 2002)

MEs lead to undesirable consequences as ADRs, drug-drug interactions (DDIs), lack of efficacy, suboptimal adherence and poor quality of life of the patient, and patient experience. Furthermore, health and financial outcomes may result including the increased use of health services, preventable medication-related hospital admissions and death. (Masotti, 2010)

MEs can be fatal. Finding from a review for FDA's Adverse Event Reporting System during 1993-1998, showed that 68.2% of the reported MEs resulted in serious patient outcomes and approximately 10% were fatal. Types of MEs that caused death were administering an improper dose, administering the wrong drug, and using the wrong route of administration. The causes that mostly results in errors were performance and knowledge deficits and communication errors. (Phillips, 2001)

The occurrence of MEs may be reported at any stage of the medication process (prescription, storage, preparation, handling, application of drugs). Most often MEs occur at drug administration stage (57.5% of all errors) and prescription stage (18.5%). (Krähenbühl-Melcher, 2007)

1.2.1 Classification of medication errors

Classification of MEs is depending on which stage of the medication use cycle they occur (prescribing, dispensing, or administration). (Williams, 2007) According to this, MEs were classified into five main classes: prescribing, transcription, dispensing, administration, and "across settings". (Van den Bemt, 2000)

Prescribing errors: are errors included at the process of selecting and prescribing a drug and on monitoring of therapy. Prescribing errors are sub-classified to administrative and procedural errors, Dosage errors, and therapeutic errors.

- **Administrative and procedural errors:**
    - General (readability)
    - Patient data (patient mix-up)
    - Ward data and prescriber data
    - Drug name
    - Dosage form and route of administration
- **Dosage errors:**
    - Strength
    - Frequency
    - Dosage too high/low
    - No maximum dosage in "at need" prescription
    - Length of therapy
    - Directions for use
- **Therapeutic errors:**
    - Indication
    - Contra-indication
    - Monitoring
    - Drug-drug interaction
    - Incorrect monotherapy
    - Duplicate therapy (Allan, 1990)

Transcription errors: These errors may happen in the process of transcribing or interpreting a medication ordered by the physician. (Kelly, 1995)

Dispensing errors: At any stage of dispensing process (from receiving the prescription in the pharmacy to the supply of a dispensed medicine to the patient) dispensing error may be encountered. (Williams, 2007)

Dispensing errors are classified to:

- Wrong drug
- Wrong dosage form
- Wrong strength
- Wrong time

Administration errors: When the drug received by the patient is different from the prescribed drug, this known as administration error. These errors are made by nurses or doctors in the hospital or by the patient in the ambulatory setting (non-compliance). (Kelly, 1995)

Classification of administration errors:

- Omission
- Unordered
- Wrong preparation
- Wrong dosage form
- Wrong route of administration
- Wrong administration technique
- Wrong dosage
- Wrong time (at least 60 minutes early or late)
- Compliance/adherence (Allan, 1990)

Across setting errors: This type of error is not discussed as such in the international literature. Yet studies have been performed on this class of errors, for example when patients are admitted to or discharged from the hospital. (Williams, 2007)

1.2.2 Risk factors for medication errors

A survey done in seven countries about the factors of patient-reported MEs demonstrated that possible risk factors in 11% of patients experiencing a medication error are poor coordination of care mainly in all seven countries, cost-related barriers to medical services or medicines in six countries. Other common risk factors across countries are seeing multiple specialists, multiple chronic conditions, hospitalization and multiple emergency room visits. (Lu, 2011)

Other factors from different studies include increasing number of medications, childhood and older age, and specific medications and medications for certain disease states (dermatology, musculoskeletal, ophthalmology, oncology and immunosuppression, otolaryngologic conditions, infections and cardiovascular). (Gandhi, 2003; Bourgeois, 2010; Guthrie, 2011)

Furthermore, a study of risk factors for errors in medication prescribing for a 1 year period showed that the most common factors were alteration of drug therapy for patients with insufficient renal or hepatic function, patient history of allergy to the same medication class, using the wrong drug name or dosage form or abbreviation, incorrect dosage calculations, and atypical or unusual and critical dosage frequency considerations. (Lesar, 1997)

Another observational study of risk factors of medication administration errors (MAEs) by Tissot et al.; demonstrated that among 14.9% of MAEs incomplete or illegible prescription and nurse workload were two significant risk factors. (Tissot, 2003)

Conversely, Nguyen et al. found that nurse experience was not significant and classified the factors associated with errors depending on the drug characteristics (administration route, the complexity of preparation, drug class) and administration time. (Nguyen, 2015)

1.2.3 Medication errors in hospitalized patients

Hospitalized patients are more susceptible to MEs. The rate of MEs for inpatients patients is 22.4 %, while the rate for outpatient is 11.4%. (Thakur, 2013)

The frequency of medication errors is 5.7% of all episodes of drug administration, 6 patients affected per 100 hospitalized. Also, 7% of the reported MEs at the hospital are potentially harmful. (Barker, 2002)

A review of 60 published articles about MEs in hospitals published between 1990 and 2003 revealed that the most often MEs are at the administration stage (57.5% of all errors). Another observed MEs are an unauthorized administration of drugs (25%), drug prescription (18.5%), transcription (15%), and drug preparation (13.5%). Also, at the drug administration stage, frequent errors are omission of a dose, wrong application time, wrong dose, and wrong administration rate. (Krähenbühl-Melcher, 2007)

Another study by Barker and associates for the prevalence of MEs reached the patients in 36 hospitals, found that the most frequent errors are wrong time (43%), omission (30%), doses error (19%), wrong dose (17%), and unauthorized drug (4%). (Barker, 2002)

Classes of medications that are likely to cause MEs in the hospital include antibiotics, cardiovascular drugs, oral anticoagulants, theophylline and antineoplastic drugs (Krähenbühl-Melcher, 2007) In particular, higher rates were observed for intravenous medications involving complex preparation procedures and for anti-infective drugs. (Nguyen, 2015)

Most departments that registered maximum errors according to Thakur et al. are surgery department, followed by internal medicine and gynecology in the 500 cases administration of medicine errors. (Thakur, 2013)

1.3. Drug-drug interactions

Concurrent use of two or more drugs together may increase the chance of interaction between the drugs. (COSTA, 1991) The risk of one drug influencing the activity, the availability or the effect of a second drug is a result of multiple drug use. This is considered as drug-drug interaction (DDI). (Caranasos, 1985) DDI defines as the influence of one drug on the pharmacokinetic and/or the pharmacodynamic actions of another drug. (Farkas, 2008) This can be noted when the drug combination lead to a clinical response different from the original effects of the two drugs if given alone. (Tatro, 1992)

DDIs are an important type of preventable ADEs which can lead to patient hospitalization or even death. (Becker M. L., 2007) Also, DDIs are considered as a prescribing error and they might end with therapeutic failure or adverse effects. (Van den Bemt, 2000) A prospective analysis of 3695 patient cases showed that DDIs linked to 59.1% of the ADRs and most of the DDIs were pharmacodynamic (91.7%), 5.3% were pharmacokinetic, and 3% were mixed pharmacokinetic and pharmacodynamic mechanism. (Davies, 2009) In addition, in older adults, 31.5% of DDIs are potentially contributing to ADRs.

One of the adverse clinical outcomes of DDIs is hospital admission. A meta-analysis of the reasons for hospital admission; revealed that 7% of serious drug interactions cases caused hospital admission or for prolonged hospital stays. (Lazarou, 1998) In 2007, DDIs resulted in 0.054% of emergency department visits and 0.57% of hospital admissions. (Becker M. L., 2007) Even during hospitalization, major and moderate potential DDIs was more frequent (1.11), compared to the frequency of hospital admission (0.59) and hospital discharge (0.60). In fact, 47% of major and moderate DDIs reported at hospital discharge were originated during hospitalization. (Vonbach, 2008) Moreover, analysis of DDIs reports in the United States demonstrated that 0.12% of re-hospitalizations were caused by DDIs.

1.3.1. Risk factors for drug-drug interactions

1.3.1.1 Patient-related factors:

- **Polypharmacy:**

Disease treatment usually combined with the use of more than one drug; however, this may increase the risk of DDIs. (Juurlink, 2003). Recently, reports in the United States showed that the percentage of the population taking three or more prescription drugs has increased from 11.8% in 1988–1994 to 20.8% in 2007–2010. Also, during this period the percentage of people taking five or more drugs has increased from 4.0% to 10.1%. (Percha, 2013)

According to Goldberg et al., the percentage of DDIs risk was 13% in patients taking 2 medications, 38% in patients taking 5 medications, 82% of patients taking 7 or more medications. The study concluded that substantial risks for adverse DDIs were taking three or more medications and patients older than 50 years of age taking two or more medications. (Goldberg, 1996)

It is important to identify and follow patients exposed to polypharmacy; they should be monitored more closely to prevent events caused by drug interactions. (Bjerrum, 2008)

- **Age**:

Age considered as a core risk factor for DDIs. At any age, DDIs can be encountered, but the in older people the risk is higher because the frequency of polypharmacy is increased. in The Netherlands, 25% of the elderly outpatients taking more than 1 medication and referred to a diagnostic clinic for decreased cognition, functional dependence, or both who; were found to have ADR or decreased drug effect possibly due to a DDIs. (Aparasu, 2007)

The incidence of DDIs is increasing after the age of 44 years and the greatest incidence is for patients over 74 years of age. (Aparasu, 2007) In contrast, the risk for DDIs is common in very young patients (< 5 years) due to the immaturity of their enzymatic metabolic system. (Shapiro, 2002)

- **DDIs based on disease conditions of the patient:**

Recently, a study conducted in 2013 to evaluate the DDIs for inpatients of a teaching hospital in South India demonstrated that the greatest average number of DDIs was in patients with cardiovascular disease with comorbid conditions, followed by cardiovascular disease (without comorbid conditions). In more details, patients with cardiovascular and respiratory disease conditions had the greatest average number of DDIs (7.33), followed by prescriptions of patients with cardiovascular disease (6.34) then hepatic disease prescriptions (6.00). (Kulkarni, 2013) Added to this, the risk of DDIs is high and common for patients with chronic renal failure (CKD) with another diseases; commonly hypertension and cardiovascular diseases. (Rifkin, 2010) Another disease combined with risk for DDIs is congestive heart failure (CHF). The drugs used in CHF are essential for pharmacologic improvements and physicians cannot exclude any of them. Polypharmacy in the treatment of CHF is unavoidable and patients may develop adverse cases as hypotension, hyperkalemia, and renal insufficiency. (Flesch, 2006) In addition, patients with cancer are frequently taking many medications for cancer treatment, drug-induced toxicity and cancer-related syndromes, and to treat other comorbidities. So they are at risk to have DDIs. (Riechelmann, 2007)

Other risks are female sex (women are also at higher risk than male), genetics, organ dysfunction, use of a medication having a narrow therapeutic index (as warfarin, digoxin, and cyclosporine), metabolic or endocrine risk conditions (as hypothyroidism, hypoproteinemia), and acute medical issues (as dehydration). (Aparasu, 2007), (Shapiro, 2002), (Goldberg, 1996), (Tulner, 2008)

1.3.1.2 Practice-related risk factors

Patient consulting different doctors had a chance to DDI. (Bjerrum, 2008) Increased number of physicians or pharmacists involved with the dispensing of medication may increase the risk for DDI. (Becker, 2005) Also, in hospitalized patients, new drugs added to the current drug therapy are increasing the risk of possible drug interactions. (Heininger-Rothbucher, 2001) (Herr, 1992) (Wiesner, 1999) More on this, when computer alerts are too frequent or too infrequent and workload increased the chance of DDIs is increase. (Becker M. L., 2005)

1.3.2 Mechanisms of drug-drug interactions

Pharmacological interactions are interactions between the drugs inside the body. Pharmacological interactions are classified into pharmacodynamics and pharmacokinetic interactions. (Scott, 2013) When one drug affects the absorption, distribution, metabolism, or excretion of another drug this is so-called pharmacokinetic interaction. Additive or antagonistic clinical effects of the two drugs is defined as a pharmacodynamic interaction. (Hansten PD, 2006)

Being familiar with the mechanisms of DDIs is important for the healthcare professionals to take an appropriate action and recognize the importance of the interaction by weighing the risks and benefits to the patient. (Lal, 2008) For instance, prescribers may change the medication, dose, time and consequence of the treatment regimen. Also, when administering of combination therapy, knowing the mechanisms of any interacting drug is important for the prediction and avoidance of toxic outcomes. (Angela D. M., 2011)

Special awareness is needed when prescribing drugs with high opportunity for interactions such as anticoagulants, antiepileptics, antifungals, antibiotics, antihistamines, NSAIDs, HIV protease inhibitors, proton pump blockers, anticancer drugs, hypoglycemic agent. Furthermore, populations like elderly patients, critically ill, and patients with chronic disease should be monitored closely for DDIs because of polypharmacy or changed renal/hepatic metabolism. (Lal, 2008)

1.3.2.1 Pharmacodynamic interactions

Pharmacodynamic interactions occur between drugs with similar or opposite pharmacological effects. (Corrie, 2017)

- **Additive or synergistic pharmacodynamic interaction**

When the effect of two drugs is greater than the effect of each agent given alone (1+1=2); this interaction is considered as additive. An example of additive DDI is the combination of aspirin (antiplatelet) with heparin (anticoagulant); this may increase the chance of bleeding.

(Scott, 2013) Even drugs with different pharmacological action but have common side effect; their side effect will be potentiated. As an example, amitriptyline (tricyclic antidepressant) and thioridazine (antipsychotic), both drugs have anticholinergic effects and can result in heat stroke in hot, humid climates or psychoses, in addition to the common side effects like dry mouth and blurred vision. Similarly, adverse effect of two drugs may also be additive as ototoxicity when using ethacrynic acid and streptomycin or nephrotoxicity when using tobramycin and cephalothin. (Pleuvry, 2005) However, the pharmacodynamic interaction may be aimed, if the drug's effects are to the same direction, this will lead in potentiating their effect (synergistic effect). (Cascorbi, 2012) More specifically, synergism occurs when the effect of two combined drugs exceeds the sum of the effects of each drug given alone (1+1=3). This interaction is aimed particularly in the use of antibiotics. (Scott, 2013) For instance, sulphonamide antibiotics and trimethoprim are bacteriostatic but when combined their effect will be bactericidal. (Pleuvry, 2005) In contrast, the combination of nitroglycerin, isosorbide (nitrates) and sildenafil may result in unwanted synergistic DDI and life-threatening drop in blood pressure.

- **Opposing or antagonistic pharmacodynamic interaction**

  When one drug diminishes or eliminates the effect of another this DDI, this interaction is defined as antagonistic (1-1=0). This DDI occur at the receptor level. Co-administration of a beta-agonist (as albuterol or salmeterol), with a beta-blocker (as propranolol or metoprolol) may reduce the effects of both drugs by competing for the same. (Scott, 2013)

  In addition, when two drugs work on different receptor systems, exert opposite effects on different receptor systems and physiologically oppose the function of one another; this considered as functional antagonism. Hyperglycemia caused by glucocorticoids may oppose the actions of hypoglycemic agents.

- **Alteration in drug transport mechanisms**

  Competition of drugs with each other for uptake at the site of action is a mechanism for DDIs. An example of this type is noradrenergic receptors. Drugs that work by noradrenaline reuptake mechanism used with tricyclic antidepressants that inhibit this reuptake process may decrease the action of drugs requiring it.

- **Changes in fluid and electrolyte balance**

In the treatment of heart failure and edema, digitalis and loop diuretics are used. Loop diuretics lower plasma K+ and as a result digitalis toxicity may increase. (Pleuvry, 2005) Often, pharmacodynamic interactions are an important concern for elderly patients due to changes in homeostatic mechanisms so they become more sensitive to the combined drug actions. Elderly patients with impaired physiological functions the additive DDIs are particularly important. Elderly men with pre-existing prostatitis may have urinary retention when two or more drugs with anticholinergic activity (as tricyclic antidepressants and antihistamines) have been used in combination. (Seymour, 1998) Also, elderly patients using NSAIDs have an estimated relative risk of peptic ulcer of 4.1 (Griffin, 1991), while in comparable patients using corticosteroids the relative risk was only 1.1. Thus, the combination of both drugs increases the risk for peptic ulcer disease to 15-fold comparing to nonusers of either drug. (Piper, 1991)

1.3.2.2 Pharmacokinetic interactions

Pharmacokinetic interactions occur when one drug interfere with the absorption, distribution, metabolism or excretion (collectively known as ADME) of the other drug. (Corrie, 2017)

- **Drug absorption interactions**

Interactions at drug absorption level may lead to subtherapeutic serum concentration of the interacting drugs and occur due to the following factors:

Changes in gastrointestinal pH:

H2-receptor blocker, proton pump inhibitors, and antacids containing Al/Mg change the gastric pH and it may significantly reduce the bioavailability of other drugs. As a result, gastric acid modifying agents may reduce the absorption of ketoconazole, itraconazole, and salicylic acid. (Lal, 2008)

Changes induced by chelation and adsorption:

Chelating lead to the formation of complexes which may affect the absorption of one of the two combined drugs. Metal ions (as calcium, magnesium, aluminum, iron) founded in antacids, preparations containing magnesium salts, aluminum and calcium preparations can decrease the absorption of tetracyclines (as doxycycline or minocycline) in the digestive tract by the formation of complexes that are poorly absorbed. (Bokor-Bratić, 2000)

Changes in gastrointestinal motility

Increase the gastric motility can reduce the absorption of a drug by decreasing the time in which the drug will be in contact with mucosal area of absorption. For example, metoclopramide reduce the absorption of digoxin and theophylline because it speeds up the gastric emptying. (Johnson, 1984)

Transporter based interactions

Multidrug efflux transporters such as P-glycoprotein (P-gp) are involved in this type of DDIs. Induction or inhibition of these proteins also results in DDIs. Rifampicin is P-gp inducer and may lead to the reduction of digoxin its plasma levels (Greiner, 2002); while verapamil is P-gp inhibitor and increases the digoxin levels. (Lal, 2008)

- **Drug distribution interactions**

Often, transportation of drugs id mediated by binding to plasma and tissues proteins such as albumin, α1-acid glycoprotein, and lipoproteins. (Palleria, 2013) Competition for plasma protein and displacement of a drug from its binding site results a transient increase the concentration of free (active) drug. (Scott, 2013)

Co-administration of warfarin and diclofenac shows pharmacological displacement interaction. Since, warfarin and diclofenac have the same affinity for albumin, using diclofenac in patients previously used warfarin for a long time may displace the warfarin from its binding site and increases the plasma concentration of free warfarin. As a consequence, serious hemorrhagic reactions may be developed. (Palleria, 2013)

- **Drug metabolism interactions**

The cytochrome P450 (CYP450) family is involved in most DDIs. CYP isoforms commonly mediate DDIs are CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. (Gad, 2008) Many DDIs are related to the inhibition or induction of CYP enzymes.

Effect of enzyme induction on drug-drug interactions:

Inducers of CYP450 increase the rate of metabolism and facilitate the clearance of the substrate from the system because inducers stimulate the production of the CYP isoform. Thus, the response to the substrate decreases and the drug will be ineffective.

Therefore, the induction of CYP450 by rifampicin, phenytoin, carbamazepine, barbiturates, glutethemide, troglitazone, rifabutin, griseofulvin and St John's Wort; lead to clinically significant DDIs when co-administered of CYP450 substrates such as warfarin, ketoconazole, itraconazole, quinidine, verapamil, mexiletine, low dose oral contraceptives, prednisolone and theophylline. This interaction lead to decrease the plasma levels of the substrates. (Lal, 2008)

Effect of enzyme inhibition on drug-drug interactions:

On the other hand, CYP450 inhibitors reduce the metabolism and extend the activity of the substrate. This may increase toxicity especially if the drug affected has a low therapeutic index, such as phenytoin. (Gad, 2008) CYP1A2 inhibitors can promote the toxicity risk of theophylline or clozapine; CYP2C9 inhibitors promote the toxicity risk of phenytoin and warfarin; while CYP3A4 inhibitors promote the toxicity risk of a larger number of drugs like carbamazepine, lovastatin and simvastatin, rifabutin, cisapride, cyclosporine, ergot, protease inhibitors and alkaloids. (Lal, 2008)

Many of the commonly prescribed drugs their clearance is mediated by the CYP3A family, particularly CYP3A4. (Gad, 2008) For instance, Ketoconazole is a selective inhibitor for CYP3A4 that responsible for the metabolism of cyclosporine. This interaction is common in transplant patients. As a result, less than 25% of the dose of cyclosporine is needed if ketoconazole is co-administered. (Pleuvry, 2005)

- **Drug elimination interactions**

Drugs are eliminated mainly by kidney and bile, but bile elimination has no significant DDIs. (Lal, 2008) Alterations of renal excretion mediated by changes in protein binding (discussed before), or inhibition of tubular secretion, or changing in the kidney blood flow or urinary pH. The action of penicillin is prolonged by the co-administration of probenecid is the classical. Probenecid was designed to compete with the active transport mechanism that secretes acids (penicillins) into the renal tubule. Other acidic drugs as aspirin, indometacin, and sulphonamides; if co-administered together the plasma concentrations of each other will be increased. NSAIDs inhibit prostaglandin production which important for renal capillary vasodilatation. As a consequence, the renal blood flow may be reduced. This interaction is significant for renally excreted drugs with a low therapeutic index, such as lithium. (Scott, 2013)

1.3.3 Role of clinical pharmacist in drug-related problems and drug-drug interactions

Clinical pharmacy is a health specialty that involves the roles and services of the clinical pharmacist to develop and promote the rational and appropriate drugs and devices use. (ESCP, 2006) More specifically, clinical pharmacy services are oriented to the patient care and aimed to reduce irrational prescribing (Lipton, 1994) (Hanlon J. T., 1996), improve disease management (Bogden, 1998) (Donovan, 2006), reduce ADEs (Schnipper, 2006), reduce length of stay, ADRs and mortality (Bond C. A., 2006), and give economic benefit (Dooley, 2004). The core practice clinical pharmacy in DRPs involve the detection of DRPs, solving, and prevention. Also, pharmacist has a major role in documenting ADRs. (Palanisamy, 2009) In addition, the assessment of DRPs by clinical pharmacists is applicable in different settings as in hospital multidisciplinary teams, nursing homes, and primary care. (Viktil, 2008) Nevertheless, identifying and resolving clinically important DRPs by pharmacist's role is most valuable in hospital settings. Collaborative drug therapy in hospital is a service of clinical pharmacy that involves cooperation between physicians and pharmacists on the drug therapy of individual patient. The collaboration results in optimizing the patient's drug therapy and quality of life. (Gattis, 1999) This can be explained based on pharmacists' extensive knowledge of medicine; they can correlate the symptoms appeared in the patient to the possible adverse effects of the drug therapy. Furthermore, clinical pharmacists reduce the incidence of ADRs by their ability to avoid drugs with potential side effects in susceptible patients. (Palanisamy, 2009)

In fact, pharmacist's contributions in DRPs are used to evaluate their role in optimization of drug therapy; because this evaluation includes determining the number of DRPs addressed or prevented, or by assessing the clinical outcomes for the patients. (Viktil, 2008) Hanlon et al showed that inappropriate drug prescribing and ADRs was minimized by the revision of the patients drugs by the pharmacist along with the discussions with physicians during the 12 months follow up period. (Hanlon J. T., 1996)

Another role of clinical pharmacists is to counsel the patients before discharge in order to detect DRPs during and after hospitalization. By this, they can identify and resolve medication discrepancies, and screen for nonadherence, and expected ADEs after discharge. (Schnipper, 2006) In addition, an important approach of the pharmaceutical care to reduce DRPs is to assess the prevalence of clinically significant DDIs and specify patients at risk during visits. (Aparasu, 2007)

In chronic diseases; for example asthma and COPD; pharmacist's responsibilities to avoid DRPs in the treatment includes evaluating therapy outcomes and benefits, referring to a physician when there are worsening signs, providing patient education on disease and medications, assessing all drugs used by patients, checking drug interactions, providing interventions, monitoring inhaler use technique, interviewing patients regarding medication adherence, immunization and smoking cessation. (Apikoglu-Rabus, 2016)

1.4. Chronic diseases

Chronic diseases are defined as "progressive and uncured illnesses or conditions". (Wu, 2000) The incidence of chronic diseases globally is continuously increasing at a rate of 16-44%. Age, advanced lifestyles and eating habits are the main factors for this incidence. (Yach, 2004) Low- and middle-income countries carry the most of the total global burden from chronic diseases in middle age, and especially from vascular diseases. (Yusuf, 2001)

Worldwide, the largest cause of mortality is chronic diseases. Chronic diseases (cardiovascular disease, cancer, chronic respiratory disease, and diabetes) have been caused 29 million deaths worldwide in 2002. (Yach, 2004) The occurrence of deaths due to chronic diseases has been increased during 2008 to 57 million deaths (63% of deaths). (Alwan, 2010) According to WHO, the main cause of death among 35 million deaths worldwide was a chronic disease. The highest chronic condition leaded to death was cardiovascular diseases (30%); mainly heart disease (coronary artery disease CAD or ischemic heart disease IHD) and stroke. The next chronic condition caused death was cancer (13%), followed by other chronic diseases as mental disorders, vision and hearing impairment, oral diseases, bone and joint disorders, and genetic disorders. Later, chronic respiratory disease (7%); commonly chronic obstructive respiratory disease (COPD) and asthma, and Diabetes (2%) were also reported to cause death. (WHO, 2005) In this study, the chronic conditions included have been selected from the list of chronic diseases which are the major cause of death and disability worldwide by WHO; with excluding cancer, as mental disorders, vision and hearing impairment, oral diseases, bone and joint disorders, and genetic disorders according to the design of this study.

In Turkey, the incidence of chronic diseases and their risk factors is increasing. A cross-sectional survey "Chronic Diseases and Risk Factors Survey" have been conducted to evaluate chronic diseases and their risk factors. The key findings showed the prevalence of hypertension was 17%, diabetes rate was 8%, cardiovascular Diseases (angina pectoris incidence was 6,4% in male and 9,8% in female; acute myocardial infarction incidence was reported by 2,3% of males and 1,1% of females; coronary heart disease incidence was 3,8% in males and 2,3% in females; cerebrovascular disease incidence was 1,8% in males and 2,2% in females), COPD prevalence was 5.0 %, and asthma 4.5%. (Ünal, 2013)

1.4.1. Drug-drug interactions in chronic diseases

DDIs are a common risk factor for patients with chronic diseases. This mainly explained by the fact that more than one drug may be prescribed for the treatment of one chronic disease. Also, the presence of comorbidities that require more drugs increase the chance for DDIs.

Polypharmaceutical combination therapies used in the treatment of chronic diseases are the most common cause of DDIs. (Sharifi, 2014) Along with increasing the number of drugs the probability of DDIs is increasing. A study showed that patients using 2 drugs were 13 % expected to develop a DDI; while patients using 5 drugs had 40 % incidence of DDIs, and the incidence exceeded 80 % for patients using 7 or more medications. (Grattagliano, 2010)

Drug regimens for patients with multiple comorbid chronic conditions commonly have interacting drugs. (Field, 2004) For instance, Diabetic patients may have another comorbid chronic illness. Thus they use additional medications rather than anti-diabetic agents. (Sankar, 2015)

Added to this, prescribers in modern practice tend to recommend high number of drugs to treat the comorbidities and patients visit multiple physicians with different specialties; potential DRPs are expected. (Adepu, 2016) Thus, increase the number of prescribers involved in the treatment of one patient, eventually increase the number of prescribed drugs; and the risk of DDIs will be increased because it may be difficult for the physicians to be aware of all drugs. (Tamblyn, 1996) According to Barat and associate, more than one prescriber are involved in the treatment of 31% of elderly patients, and the prescribers were not able to aware of about 25% of prescribed drugs used by their patients. (Barat, 2000)

Older patients have high risk DDIs because they have a high incidence of chronic diseases and comorbidities. So, they need multiple medications to treat their conditions. (Salive, 2013)

Drugs used for the treatment of chronic diseases are consumed for a long term. As a consequence, the risk of DDIs may be increased. Especially with cardiovascular drugs which are the most common group that interact with other drugs. A study for drug interactions on new or refill prescriptions; demonstrated that highest prevalence of DDIs is reported with

cardiovascular drugs as diuretics, ACEIs, and B-blockers. (Indermitte, 2007) In contrast, anticoagulants as warfarin are the most drug group caused 92 % of DDIs. (Aparasu, 2007)

Many drug interactions encountered with the treatment of multiple chronic diseases cannot be avoided. An example of this case is the co-administration of aspirin and ACEI is recommended by most guidelines in patients with cardiovascular disease. However, their interaction may lead adverse effect on renal function. Likewise, patients with renal insufficiency and osteoarthritis are usually prescribed with NSAIDs and ACEI that affect renal function. (Bjerrum, 2008)

1.5. Previous studies

In 2015, a cross-sectional observational study carried on three community pharmacies in Mysuru city to asset the DDIs in patients with chronic disease. 800 prescriptions were reviewed and 500 potential DDIs were detected. The prevalence of DDIs interactions among the prescriptions was 39.37%. The highest reported potential DDIs were beta-adrenergic blockers and oral hypoglycaemic (22.4%), then beta-blockers and dihydropyridine calcium channel blockers (10.6%). (Jaskumar, 2015)

A study in a teaching hospital in South India was conducted to assess the DDIs through prescription analysis prospectively for inpatients during a period of 6 months. Over 204 prescriptions, 91% of them had a total number of 856 DDIs. Most frequently DDIs were moderate (70%) followed by minor (28%). Through the analysis of the results, chronic diseases were involved. Patients with cardiovascular and respiratory disease conditions had the greatest average number of DDIs (7.33), then cardiovascular disease (6.34), then hepatic disease prescriptions (6.00). (Kulkarni, 2013)

Adepu and Adusumilli carried out a prospective study in 2015 to evaluate the incidence, prevalence, and cost implications of DRPs in patients with chronic diseases. The study was conducted in a south Indian rural community during a period of 9 months. Among over 90 DRPs identified in 215 patients; 14 (20%) DDIs were reported. Hypertension was the most chronic condition combined with the greatest number of DDIs (8 interactions), followed by asthma with hypertension (2 interactions). (Adepu, 2016)

Since the disease and regimen of hospitalized cardiac patients is complex, they require more attention for DDIs. A cross-sectional descriptive study conducted in Cardiology Department of the Ayub Teaching Hospital during a period of 1 year. The study aimed to evaluate potential DDIs and its associated factors in cardiac patients. %109 potential DDIs were identified among 2342 patients. At least one potential DDI was detected in 91.6% of the patients. Most of the DDIs were moderate (55%) followed by major (45%). (Murtaza, 2016)

A study of DDIs in hospitalized diabetic patients was carried out in Coimbatore, India. Among 50 prescriptions, DDIs were observed in 35 (70%) prescriptions. The highest DDI

percent was for cardiovascular drugs (92%), then analgesic drugs (66%), antibiotics (52%), antidiabetic drugs (26%), diuretic drugs (26%), and finally antipsychotic drugs (24%). (Sankar, 2015)

Moreover, Roblek et al. retrospectively evaluated the DDIs in admission drugs and discharge drugs for hospitalized patients with COPD. Results showed 90% of the patients had at least one interaction. Also, the dominant type of DDIs among patients was type C interaction, then type D, and finally type X. The number of DDIs was more at hospital discharge in compare to hospital admission for all types of interactions. (Roblek, 2012)

Recently, in 2018, a prospective study evaluating DDIs in hospitalized patients at the cardiac and pulmonary departments during a 1 year. The total number of enrolled patients was 1150, in which 685 were cardiac and 465 were pulmonary patients. On average, mostly cardiac patients are diagnosed with hypertension (31.48%), followed be angina with diabetes mellitus (21.18%). While pulmonary patients are commonly diagnosed with asthma (21.73%). In cardiac patients, 856 potential DDIs were found, and 675 potential DDIs were found in pulmonary patients. The most common combination of drugs that caused DDI was aspirin and clopidogrel through 245 cardiac patients, whereas ranitidine-theophylline combination was the highest among pulmonary patients with 195 DDIs. (Ramalingam, 2018)

Furthermore, the DDIs were assessed for hospitalized patients in the pulmonology department in a prospective study using Micromedex drug checker software and drugs.com. According to the study, 18 interacting pairs were reported among 265 interactions. The incidence of DDIs increases with increased age and hospital stay days. (Kameswaran, 2017)

Another study by for DDIs in hospitalized patients at the medical unit found that the most commonly DDIs were moderate and frequently occur for patients prescribed with cardiovascular drugs. The commonly DDIs were fluoroquinolones and oral antidiabetics, iron and pantoprazole, aspirin and clopidogrel. (Soherwardi, 2012)

1.6. Aim of the study

The main objectives of our study were to assess the frequency of drug-drug interactions in patients with chronic diseases during the period of hospitalization, to find the severity levels and risk rates of occurring drug-drug interactions, to identify the most common drugs combinations that cause drug-drug interactions among the patients, and to evaluate the risk factors associated with drug-drug interactions in hospitalized patients with chronic diseases.

2. METHODOLOGY

A cross-sectional retrospective observational study was conducted in hospitalized patients at Near East University (NEU) Teaching Hospital in Northern Cyprus from 01 April to 01 June, 2018. The prescriptions were collected for male and female patients with chronic diseases (chronic cardiac diseases, Diabetes mellitus, asthma and COPD) admitted to cardiology unit, internal medicine unit and chest diseases and allergy unit during the study period. The data was obtained from the patient's records. Only the last prescription for each patient during hospitalization has been evaluated. Drug-drug interactions were screened using Lexi-Interact tool of Lexi-comp. This study was approved by the Near East Institutional Reviews Board (IRB) of Near East University Hospital.

2.1 Inclusion criteria

1) Patients hospitalized at Near East University Hospital during the period from 01 April to 01 June, 2018.
2) Patients suffering from at least one of chronic diseases (chronic cardiac diseases, diabetes mellitus, asthma and chronic obstructive pulmonary disease.
3) Patients admitted to cardiology or internal medicine or chest diseases and allergy departments.
4) Patients using more than one medication.
5) Patients who are adult (age > 19 Years) and older.
6) Patients with a complete medical record.

2.2 Exclusion criteria

1) Patients who were at intensive care unit (ICU).
2) Patients with incomplete files.

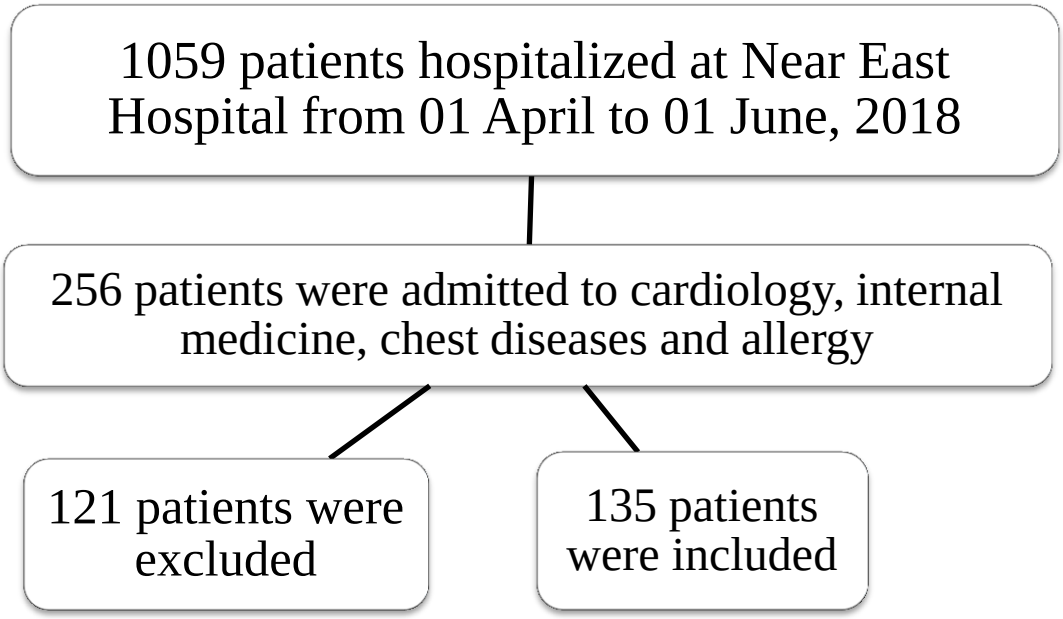

Figure 2: Inclusion and exclusion pattern of the patients.

2.3 Sample size and data collection

A total number of 1059 patients have been hospitalized at NEU Hospital from 01 April to 01 June, 2018. 256 patients were admitted to the cardiology unit, internal medicine unit and chest diseases and allergy unit. Overall, 135 patients were included in the study and eligible for analysis whereas 121 patients were excluded.

The chronic conditions included have been selected from the list of chronic diseases which are the major cause of death and disability worldwide by WHO (Cardiac diseases, Diabetes mellitus, asthma, and COPD. (WHO, 2005)

The data were retrieved from patient's medical record and collected in a specially designed data entry format. The following information was collected: patient's age, gender, date of admission, number of hospital stay days, current diagnosis, past medical conditions, drugs during administration and drugs during hospitalisation. Other information includes pharmacological classification of the drugs and frequently occurring DDIs.

2.4 Identification of drug-drug interactions

Collected retrospective data was analyzed using Lexi-Interact tool of Lexi-Comp, (Wolters Kluwer Clinical Drug Information, Inc.). 2018. This is powered by Wolters Kluwer Health. The severity and the risk rate of the DDIs were checked also using Lexi-Interact. Identified DDIs were classified according to the severity into major, moderate and minor. Mechanisms of DDIs were categorized based on the data in Lexi-Interact to pharmacodynamic, pharmacokinetic, unclear and unknown. The pharmacodynamic and pharmacokinetic were primary considered in the results of this study. According to Lexi-comp, major indicates a life-threatening or permanent damage due to the interaction; moderate severity indicates deterioration of patient's condition and additional care or extended hospitalization may be required; minor severity indicates an annoying interaction but not medically harmful. Risk rates of DDIs were divided into 5 categories (A to X). [Table 2] The risk rates of X, D, and C were clinically important and accounted in the discussion of this study.

Lexi-comp is most extensive drug database, with content that addresses all patient populations and covers clinical specialties such as pharmacy, internal medicine, cardiology, oncology, psychiatry, anesthesiology and more.

Lexi-comp contains over 25 items, including 6 sources of monographs on prescription and over-the-counter drugs, 2 books on international monographs, and single books focusing on herbal monographs, patient education for adult and pediatric populations, pregnancy and lactation, toxicology, drug allergies, lab and diagnostic tests, and pharmacogenomics. Interactive tools include a pill identifier, oral and topical drug interaction tool, more than 100 clinical calculators, and 2 intravenous-drug interactions tools. (Chatfield, 2015) An evaluation of resources for analyzing drug interactions by Petal et al., suggested that scope scores were higher for Lexi-comp Interactions (97.0%) compared to all other resources. Also, completeness scores of Lexi-comp were high. (Patel R. I., 2016) Another study compared different DDIs screening software the programs' sensitivity, specificity, and accuracy, demonstrated Lexi-Interact was the most accurate software and had the best performance. (Kheshti, 2016)

Table 2: Risk rating categories by Lexi-comp (www.webstore.lexi.com; Wolters Kluwer)

Risk rating	Action	Description
A	No interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents
B	No action needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.
C	Monitor therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Modify regimen	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, choosing alternative agents.
X	Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

2.5 Statistical analysis

The collected data was entered in Microsoft Office Excel 2010 and analyzed by using Statistical Package for the Social Sciences (SPSS) statistical software version 18.0.

Descriptive statistic was used to analyze continuous data while crosstabs and correlation test used for categorical data. The continuous data was presented by mean ± standard deviation, median, and ranges. The categorical variables were presented by frequencies and percentages. Chi-square, Mann-Whitney Test, and correlation tests were applied to determine the p-values for specific risk factors of DDIs (age, gender, presence of chronic diseases, length of hospital stay, number of administered medications, and chronically and acutely used drugs). A p-value of <0.05 was considered as statistically significant.

2.6 Ethical consideration

Confidentiality was assured during the study and also patients' privacy. The study was approved by the Near East Institutional Reviews Board (IRB) of NEU Hospital that assigned this research as being just observational study and just initials were used during the study.

3. RESULTS

3.1 Characteristics of the patients

3.1.1 Demographics

A total of 1059 patients were hospitalized at Near East Hospital during the period of this study. Among them, 135 patients were included and studied. Of the studied patient 81 (60%) were male and 54 (40%) were female. Most patients were between 65 and 84 years of age (57.8%). The median age was 70 (mean age 68.39 ±12.7 years). The range of hospital stay was 1 to 27 days (3.24 ±4.16). Commonly, patients were hospitalized for 1-2 days (64.4%). [Table 3] of included patients, 89 (65.9%) patients were at cardiology department, 23 (17%) from internal medicine department, and 23 (17%) from chest diseases and allergy. [Figure 3]

3.1.2 Prescription pattern of drugs

The patients have prescribed a range of between 2 to 19 drugs (7.87 ± 3.5). The highest percentage of patients were taking 5 to 10 drugs (60%). The total number of drugs prescribed to 135 patients was 1062; with a median of 8 drugs. [Table 3]

3.1.3 Disease wise distribution of the patients

The patients were included in this study were diagnosed with a chronic disease; mainly chronic cardiac diseases, diabetes mellitus, asthma, COPD, and other chronic conditions. Of the chronic disease in the patients, 125 cases were chronic cardiac diseases, 45 cases were diabetes mellitus, 5 cases were asthma, 11 cases were COPD, and 63 other chronic conditions. [Table4]

Table 3: General demographic characteristics of the patients.

Characteristics	Frequency *n*	Percent %
Gender		
Male	81	60%
Female	54	40%
Age (years)		
18-29	1	0.7%
30-39	0	--
40-64	46	34.1%
65-84	78	57.8%
≥ 85	10	7.4%
Hospital stay (days)		
< 3	87	64.%
3-7	34	25.2%
>7	14	10.4%
Prescribed medications per patient		
2-4	27	20%
5-10	81	60%
>10	27	20%

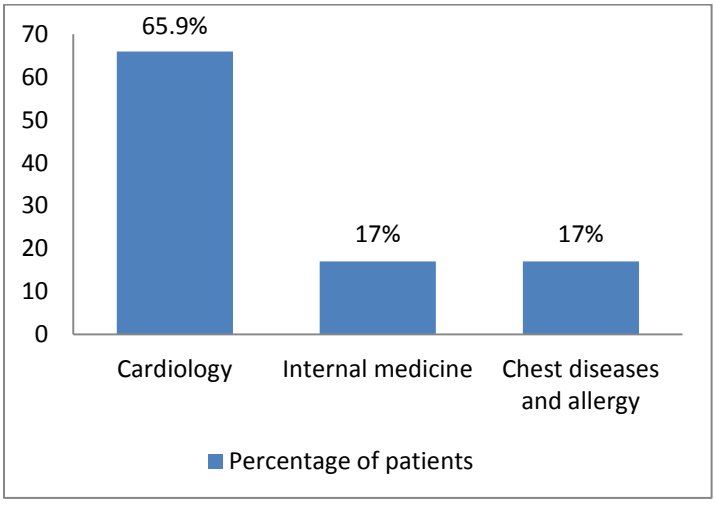

Figure 3: Distribution of the patients across hospital departments.

Table 4: Disease distribution of the patients and classification of diseases and related health problems (ICD 10) of the chronic diseases.

Characteristics	Frequency of cases among the patients *n* (%)	ICD 10 code
Main diagnosis		
Chronic cardiac diseases	125 (50.2)	-
- **Hypertension**	91 (36.9)	I10
- **Myocardial infarction (MI)**	10 (4)	I21
- **Heart failure (HF)**	23 (9.3)	I50
- **Atrial fibrillation (AF)**	21 (8.5)	I48
- **Chronic ischemic heart disease**	45(18.3)	I25
- **Cardiac and vascular implants and grafts (CABG, stent, and prosthetic heart valve)**	46 (18.6)	Z95
- **Venous thromboembolism (VTE)**	5 (2)	Z86
- **Angina**	5 (2)	I20
Diabetes mellitus	45 (18)	E11
Asthma	5 (2)	J45
COPD	11 (4.4)	J44
Other chronic conditions	63 (25.3)	-

ICD 10: Classification of Diseases and Related Health Problems; CABG: Coronary Artery Bypass Graft.

3.2. Drug-drug interactions data

Out of 135 patients, 119 (88.1%) patients were having DDIs and 16 (11.9%) patients with no DDIs. [Table 4] Each patient had 6.2 ±6.5 DDIs. Among the 119 patients with DDIs, 70 (58.8%) patients were male whereas 49 (42.2%) patients were female. [Table 6] During the study period, the total number of the prescribed drugs was 1062. Overall, 703 drugs were reported to interact. The most frequent type of drugs associated with DDIs were drugs prescribed for chronic use in a total of 507 drugs (3.76 ±3); then drugs prescribed for acute use in a total of 196 drugs (1.45 ±1.75). [Figure 4] In total, 840 pairs of DDIs were found in the included patients. The average DDI per patient was 6.22 ±6.5. Patients admitted to the cardiology unit have a higher incidence of DDIs 77 (64.7%) than patients in the internal medicine and chest diseases and allergy. [Table 7]

Table 5: Frequency of drug-drug interactions among the patients.

Presence of DDIs	Frequency	Percent
No	16	11.9%
Yes	119	88.1%
Total	135	100.0%

DDI: Drug-Drug Interactions

Table 6: Distribution of drug-drug interactions according to gender.

Gender		DDI	
		No	**Yes**
Male	Count	11	70
	% within Gender	13.6%	86.4%
Female	Count	5	49
	% within Gender	9.3%	90.7%
	Total count	16	119

DDI: Drug-Drug Interactions

Table 7: Distribution of drug-drug interactions according to the hospital departments.

Department	Drug-drug interactions N(%)
Cardiology	77 (64.7%)
Internal medicine	21 (17.6%)
Chest diseases and allergy	21 (17.6%)

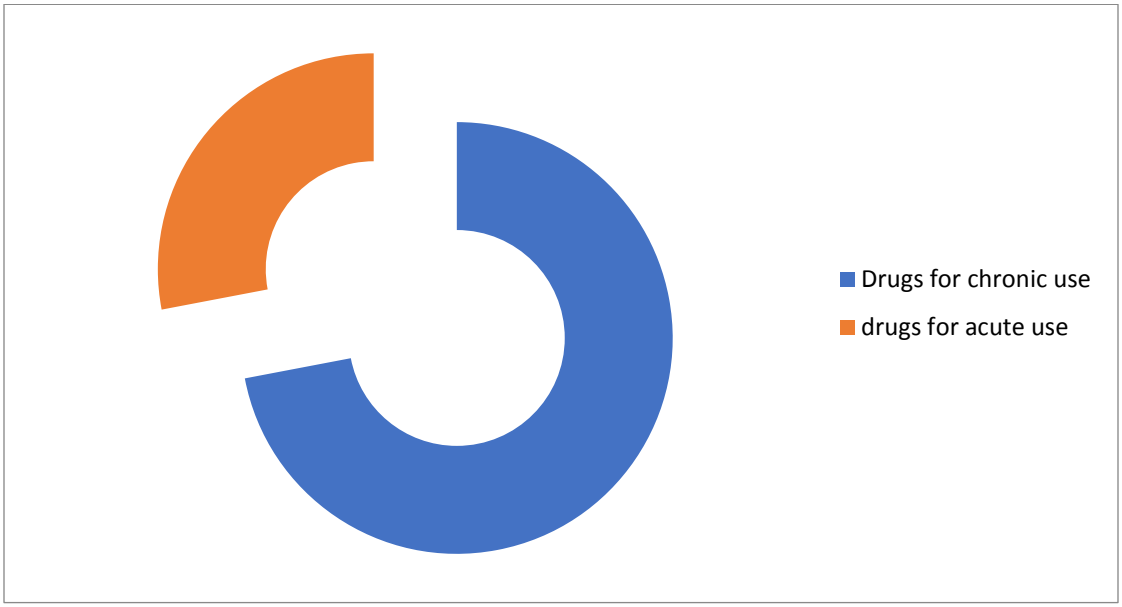

Figure 4: Types of reported drugs with drug-drug interactions.

3.3. Types of drug-drug interactions

The information about the reported DDIs where noted according to Lexi-interact tool by Lexi-comp. Based on the mechanism of interaction, the most frequent interactions was pharmacodynamic 518 (3.84 ± 4.6), followed by pharmacokinetic interactions 305 (2.26 ± 2.9). [Table 8] Other uncommon mechanisms for interactions were unclear (27 interactions) and unknown (9 interactions). By the severity of interaction, moderate DDIs were the most frequent (75.4%) followed by major (15.6%) and minor (7.5%). Table 6 shows the frequency of DDIs regarding the risk rating categories (A to X). The most type of interactions was C category (67.8 %). Clinical important DDIs are type X, D and C. the frequency of these types is 717 (84.2).

Table 8: Types of drug-drug interactions categorized by the mechanism of interaction, risk rate and severity.

Types of drug-drug interactions	Frequency *n*	Percent %	Per patient ±SD
According to the mechanism of interaction			
Pharmacodynamic	518	60.3%	3.84 ± 4.6
Pharmacokinetic	305	35.5%	2.26 ± 2.9
Unclear	27	3.1%	0.2 ±0.43
Unknown	9	1%	0.07 ±0.3
According to the risk rate			
X	30	3.5 %	0.22 ±0.6
D	110	12.9 %	0.81 ±1.3
C	577	67.8 %	4.27 ± 4.9
B	123	14.4 %	0.9 ± 1.2
A	11	1.29 %	0.08 ± 0.3
According to the severity			
Major	134	15.6 %	0.99 ±1.52
Moderate	646	75.4 %	4.79 ±5.4
Minor	65	7.5 %	0.48 ±0.8
N/A	11	1.2 %	0.08 ±0.3

3.4. Disease wise distribution of the drug-drug interactions

The results showed that patients were suffering mostly of cardiac chronic diseases. In 125 cases of cardiac diseases, 110 (88%) cases were associated with DDIs. 82 cases of hypertension were associated with DDIs and is considered the most frequent cardiac diseases combined with DDIs. Next, both myocardial infarction and Coronary artery bypass grafting with a frequency of 20 cases with DDIs. The following condition encountered DDIs was arterial fibrillation (n=19). [Table 9] DDIs among patients with cardiac diseases were caused mainly by the pharmacodynamic mechanism 98 (53.8%), while 84 (46.1%) of them were caused by a pharmacokinetic mechanism. 50% of these interactions were moderate in severity (102 DDIs), 29.4% were major (60 DDIs) and 20% were minor (42 DDIs). The most frequent type of interaction was type C (40%), followed by type B (24%), then type D (23%), type X (7.2%) and type A (4%).

Across the diabetes mellitus cases, 40 (88.9%) patients had DDIs. The common mechanism of these interactions was pharmacodynamic 38 (53.5%). However, the pharmacodynamic interactions counted for 33 (46.4%). Of the total DDIs in those patients, C interactions are most common 39 (42.3%). The frequency of the next common type of interaction is 22 (23.9%) for D interactions, followed by B 21 (22.8%), then X 7 (7.6%) and A 3 (3.2%). Depending on the frequencies, moderate interactions are very frequent. 26 (32.9%) were major interactions, 38 (48.1%) were moderate and 15 (18.9%) were minor.

3 (60%) patients out of 5 patients reported with asthma were having DDIs. Among 11 registered cases of COPD, 10 cases were associated with DDIs. Among the total cases of other chronic conditions founded in the patients, 47 (88.7%) cases were combined with DDIs. DDIs among those groups were caused mainly by the pharmacodynamic mechanism. Also, moderate interactions were the most common type of interaction and type C interaction was the most risk rated. More detailed data are presented in table 10.

Table 9: Drug-drug interactions distribution among patients with cardiac diseases.

Type of cardiac disease	**Frequency *n***	**ICD 10 code**
Hypertension	82	I10
Myocardial infarction (MI)	9	I21
Heart failure (HF)	20	I50
Atrial fibrillation (AF)	19	I48
Chronic ischemic heart disease	38	I25
Cardiac and vascular implants and grafts (CABG, stent, and prosthetic heart valve)	43	Z95
Venous thromboembolism (VTE)	4	Z86
Angina	3	I20

ICD 10: Classification of Diseases and Related Health Problems; CABG: Coronary Artery Bypass Graft.

Table 10: Drug-drug interactions distribution among patient's chronic conditions.

Chronic conditions	DDIs among chronic conditions		Mechanism of interactions N (%)		Severity of interactions N (%)			Risk rate N (%)				
	N (%)	Mean ±SD	PD	PK	Major	Moderate	Minor	X	D	C	B	A
CD	110 (52.3)	6.4 ±6.6	98 (53.8)	84 (46.1)	60 (29.4)	102 (50)	24 (20)	18 (7.2)	59 (23)	102 (40)	60 (24)	10 (4)
DM	40 (19)	7.4 ±7.6	38 (53.5)	33 (46.4)	26 (32.9)	38 (48.1)	15 (18.9)	7 (7.6)	22 (23.9)	21 (22.8)	39 (42.3)	3 (3.2)
Asthma	3 (1.4)	4.4 ±4.3	3 (60)	2 (40)	1 (20)	3 (75)	--	--	--	3 (3)	1 (20)	1 (20)
COPD	10 (4.7)	2.2 ±0.6	10 (52.6)	9 (47.3)	6 (27.2)	10 (45.4)	6 (27.2)	5 (17.2)	5 (17.2)	10 (34.4)	9 (31)	--
Other	47 (22.3)	2 ±0.6	39 (51.3)	37 (48.6)	26 (28.2)	44 (47.8)	22 (23.9)	7 (6)	27 (23.6)	44 (38.5)	32 (28)	4 (3.5)

DDIs: Drug-Drug Interactions; PD: Pharmacodynamic; PK: Pharmacokinetic; CD: Cardiac Disease; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease.

3.5. Drug-drug interactions related to age and gender

The patients in the age group of 65-84 years showed the highest number of DDIs 71 (59.7%) among the total 119 interactions. The frequencies of DDIs in other age groups were 1 interaction for 18-29 years aged patients (0.8%), 39 interactions in 40-64 years aged patients (33.8%) and 8 interactions in 85 and more years aged patients. In all the age groups, the widest type of risk was C. Patients aged 18-29 years had 1 (0.9%) C type of interaction, 40-64 years group had 34 (30.6%), 65-84 years group had 68 (61.3%) and 85 and more group had 8 (7.2%). Specific numbers according to the types of DDIs are presented in table 11.

The percentage of DDIs in male patients 58.8% (n= 70) were more than female patients 42.2% (n= 49). Male patients in this study were exposed mostly to pharmacodynamic DDIs 60 (58.2%). Similarly, in female patients pharmacodynamics interactions were dominant 46 (58.2%). In both groups, moderate interactions were frequently encountered (49.2% in males and 52.3% in females). C interactions were the most common through male 39.3% (n= 63) and female 43.6% (n= 48). While, A interactions were less common in both genders; males had 5% (n= 8) and females had 1.8% (n= 2).

Table 11: The distribution of drug-drug interactions according to age groups and gender.

Patient's characteristics	DDIs N (%)	Mechanism N (%)		Severity level N (%)			Risk rate N (%)				
		PD	PK	Major	Moderate	Minor	X	D	C	B	A
Age											
18-29	1 (0.8)	1 (100)	--	1 (100)	--	--	--	--	1 (100)	--	--
30-39	--	--	--	--	--	--	--	--	--	--	--
40-64	39 (32.8)	35 (51.4)	33 (48.5)	25(33.7)	35 (47.2)	14 (18.9)	5 (5.8)	23 (27)	34 (40)	19 (22.3)	4 (4.7)
65-84	71 (59.7)	64 (65.1)	50 (43.8)	37 (28.6)	67 (51.9)	25 (19.3)	17 (10)	36 (21.1)	68 (40)	43 (25.2)	6 (3.5)
≥ 85	8 (6.7)	6 (50)	6 (50)	2 (14.2)	8 (57.1)	4 (28.5)	--	2 (14.2)	8 (57.1)	4 (28.5)	--
Gender											
Male	70 (58.8)	60 (51.7)	56 (48.2)	41 (31)	65 (49.2)	26 (19.6)	9 (5.6)	42 (26.2)	63 (39.3)	38 (23.7)	8 (5)
Female	49 (42.2)	46 (58.2)	33 (41.7)	24 (27.9)	45 (52.3)	17 (19.7)	13 (11.8)	19 (17.2)	48 (43.6)	28 (25.4)	2 (1.8)

DDIs: Drug-Drug Interactions; PD: Pharmacodynamic; PK: Pharmacokinetic.

3.6. Drug-drug interactions related to the length of hospital stay

The average hospital stay day was 3.24 (SD ± 4.16) per patient. Of the total 135 patients included in this study, 64.4% (n= 87) were frequently hospitalized for 1-2 days, followed by 25.2% (n= 34) hospitalized for 3-7 days and then 10.4% (n=14) stayed for more than 7 days. Patients with less hospital stay days showed a higher incidence of DDIs.

63% (n= 75) of DDIs were detected in patients hospitalized for 1-2 days; 27% (n= 33) DDIs founded in patients hospitalized for 3-7 days and 9.2% (n= 11) in patients hospitalized for more than 7 days.

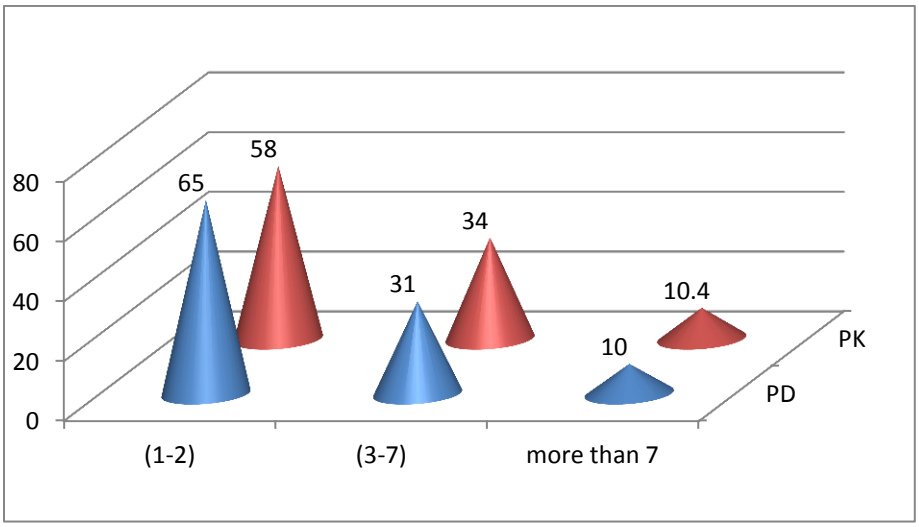

Figure 5: Distribution of pharmacodynamics and pharmacokinetic interactions by the hospital stay days.
PD: Pharmacodynamic; PK: Pharmacokinetic.

Table 12: Types of drug-drug interactions related to the length of hospital stay.

Hospital stay length	**Level of severity N(%)**			**Risk rate N(%)**				
	Major	**Moderate**	**Minor**	**X**	**D**	**C**	**B**	**A**
1-2	41 (30.5)	67 (50)	26 (19.4)	12 (7.2)	41 (8.4)	68 (40.9)	37 (22.2)	8 (4.8)
3-7	21 (31.8)	32 (48.4)	13 (19.6)	7 (8.6)	18 (22.2)	32 (39.5)	22 (27)	2 (2.4)
>7	3 (16.6)	11 (61.1)	4 (22.2)	3 (13)	2 (8.6)	11 (47.8)	7 (30.4)	--

3.7. Drug-drug interactions related to administered drugs

Patients were classified by the number of administered drugs into three groups; 2-4 drugs, 5-10 drugs and more than 10 drugs. Overall 1062 drugs prescribed in the included patients, 5-10 drugs were taken by most patients and had the largest number of DDIs 80 (67.2%) in compare to other groups; 2-4 drugs group had 12 (10.1%) DDIs and more than 10 drugs group reported 27 (22.7%). Patients using 5-10 drugs were frequently exposed to pharmacodynamic interactions 70 (55.1%) rather than pharmacokinetic interactions 57 (44.8%). The number of drugs which were prescribed and the change in the percentage of severity and risk rate of the interactions is shown in figure 6 and figure 7.

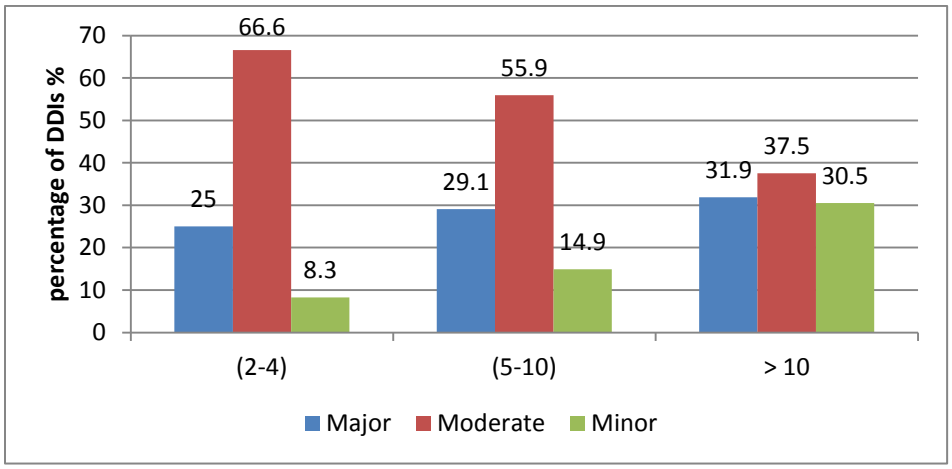

Figure 6: The percentage of severity levels according to the number of prescribed drugs.

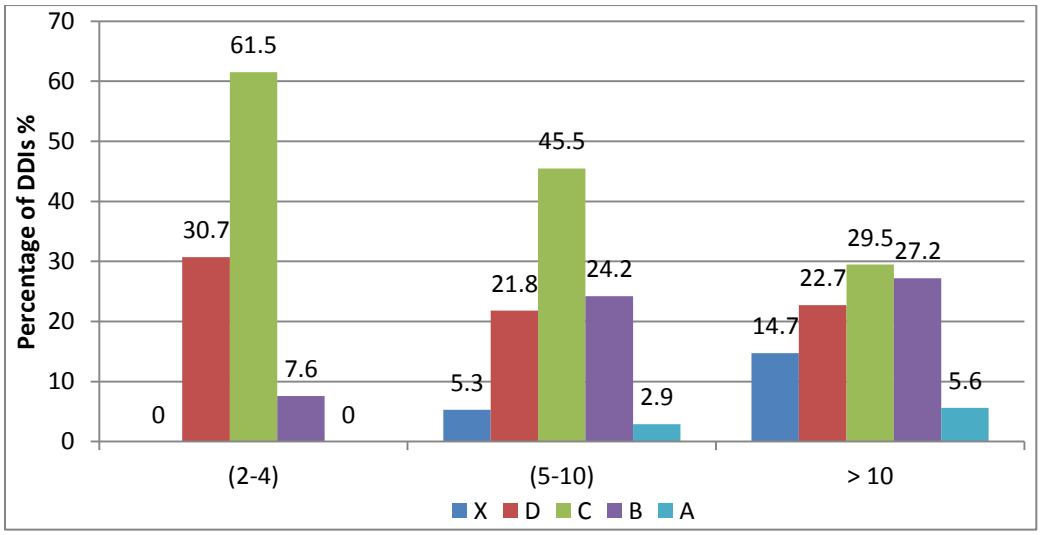

Figure 7: The percentage of risk rates according to the number of prescribed drugs.

Drugs prescribed for chronic use were resulted in a statistically significant increase in the number of DDIs ($p<0.05$) compared to drugs for acute use.

DDIs caused by chronically used drugs were 507 (mean 3.7 ± 3) while acutely used drugs caused 196 (mean 1.4 ±1.7). The number of moderate interactions was greatest in both chronically used drugs 106 (50.7%) and acutely used drugs 77 (46.6%). Pharmacodynamic interactions were the most cause of DDIs by chronic 99 (53.2%) and acute 75 (53.5%) drugs in compare to the pharmacodynamics interactions. In chronic drugs and acute drugs, C interactions were most dominant. C interactions were appeared by the use of 106 (41%) chronic drugs and 78 (37.6%) acute drugs.

Considering the concern of clinically important interactions, only type X, D and C interactions were scanned among the DDIs. The most common DDI combinations in type X interactions were cefuroxime + pantoprazole (n=3) and ipratropium/salbutamol + carvedilol (n=3). While the frequently reported type D interaction was clopidogrel + pantoprazole (n=19). Aspirin + clopidogrel drug combination was in the top of type C interactions. The rest of frequently DDIs are presented in table 13, table 14, and table 15.

Table 13: Most frequently identified type X interactions.

Interaction	*N*	Mechanism of interaction	Severity	Proposed action and recommendation	Clinical implication
Cefuroxime + pantoprazole	3	PK	Moderate	**- Avoid combination.** - Stop pantoprazole while using cefuroxime or prescribe different antibiotic.	Pantoprazole may decrease the absorption of cefuroxime.
Ipratropium/salbutamol + carvedilol	3	PD	Major	**- Avoid combination.** - The use of cardioselective agents is preferred to nonselective agents.	Carvedilol may diminish the bronchodilatory effect of salbutamol.
Amiodarone + citalopram	2	PD	Major	**- Avoid combination.** - Monitor ECG. - Monitor patients with higher risk for potentially life-threating toxicities (older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations). - Immediate medical attention if the patient developed sudden dizziness, lightheadedness, fainting, shortness of breath, or heart palpitations during treatment.	QTc-prolonging agent increase risk of ventricular tachyarrhythmias like TdP.
Escitalopram + quetiapine	2	PD	Major	**- Avoid combination.** - Monitor ECG. - Monitor patients with higher risk for potentially life-threating toxicities (older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations). - Immediate medical attention if the patient developed sudden dizziness, lightheadedness, fainting, shortness of breath, or heart palpitations during treatment.	QTc-prolonging agent increase risk of ventricular tachyarrhythmias like TdP.
Amiodarone + moxifloxacin	2	PD	Major	**- Avoid combination.** - Monitor ECG. - Monitor patients with higher risk for potentially life-threating toxicities (older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations). - Immediate medical attention if the patient developed sudden dizziness, lightheadedness, fainting, shortness of breath, or heart palpitations during treatment.	QTc-prolonging agent increase risk of ventricular tachyarrhythmias like TdP.

PD: Pharmacodynamic; PK: Pharmacokinetic; TdP: Torsade de Pointes.

Table 14: Most frequently identified type D interactions.

Interaction	*N*	Mechanism of interaction	Severity	Proposed action and recommendation	Clinical implication
Clopidogrel + pantoprazole	19	PK	Major	**- Consider therapy modification.** - Change pantoprazole to safer alternatives for stomach acid or ulcer. - Monitor INR.	Pantoprazole may decrease serum concentration of active metabolite of clopidogrel and impair its effectiveness.
Aspirin + ticagrelor	13	Unclear	Major	**- Consider therapy modification.** - Avoid maintenance aspirin doses greater than 100 mg/day. - Low dose of aspirin (75-100 mg/day) is recommended. - Monitor INR	Aspirin may enhance antiplatelet effect of ticagrelor. High dose of aspirin may diminish the therapeutic effect of ticagrelor.
Aspirin + ibuprofen	4	PK	Major	**- Consider therapy modification.** - Dose adjustment. - Monitor for GI bleeding symptoms (severe abdominal pain, bloating, dizziness or lightheadedness, nausea, vomiting (with blood), loss of appetite, and/or black, tarry stools).	- Enhance adverse effect of aspirin and gastrointestinal bleeding. - Diminish the cardioprotective effect of aspirin. - Aspirin may decrease the serum concentration of ibuprofen.
Apixaban + aspirin	3	PD	Major	**- Consider therapy modification.** - Monitor the patient closely for any unusual bleeding or bruising, or signs and symptoms of bleeding such as dizziness; lightheadedness; red or black, tarry stools; coughing up or vomiting fresh or dried blood; severe headache; and weakness. - Monitor INR.	Bleeding.
Apixaban + clopidogrel	3	PD	Major	**- Consider therapy modification.** - Monitor the patient closely for any unusual bleeding or bruising, or signs and symptoms of bleeding such as dizziness; lightheadedness; red or black, tarry stools; coughing up or vomiting fresh or dried blood; severe headache; and weakness. - Monitor INR.	Bleeding.
Amiodarone + warfarin	3	PK	Major	**- Consider therapy modification** - Adjust the dose based on PT or INR. - Monitor the patient closely for any unusual bleeding or bruising, or signs and symptoms of bleeding such as dizziness; lightheadedness; red or black, tarry stools; coughing up or vomiting fresh or dried blood; severe headache; and weakness.	Hemorrhage.

Furosemide + ibuprofen	2	PD	Moderate	**- Consider therapy modification.** - Consider using an NSAID that have lesser tendency to interact with loop diuretic (as diflunisal, flurbiprofen, ketoprofen, and ketorolac). - Monitor patient for decreased therapeutic effect of loop diuretic and alteration in fluid balance (edema). - Avoid the concomitant use of NSAID and loop diuretics in patients with HF or cirrhosis because they are more sensitive to alteration in fluid balance. - Monitor evidence for AKI with NSAID and loop diuretic combination, particularly is also used together with an ACE inhibitor.	- Diminish the diuretic effect of furosemide. - Enhance the nephrotoxic effect of ibuprofen.
Ipratropium /salbutamol + citalopram	2	PD	Major	**- Consider therapy modification.** - Monitor ECG. - Monitor patients with higher risk for potentially life-threating toxicities (older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations). - Immediate medical attention if the patient developed sudden dizziness, lightheadedness, fainting, shortness of breath, or heart palpitations during treatment.	QTc-prolonging agent increase risk of ventricular tachyarrhythmias like TdP.
Sucralfate + furosemide	2	PK	Major	**- Consider therapy modification.** - Separate administration by at least 2 hours.	Decrease serum concentration of furosemide and impair its absorption.
Moxifloxacin + escitalopram	2	PD	Major	**- Consider therapy modification.** - Monitor ECG. - Monitor patients with higher risk for potentially life-threating toxicities (older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations). - Immediate medical attention if the patient developed sudden dizziness, lightheadedness, fainting, shortness of breath, or heart palpitations during treatment.	QTc-prolonging agent increase risk of ventricular tachyarrhythmias like TdP.

PD: Pharmacodynamic; PK: Pharmacokinetic; GI: Gastrointestinal; PT: Prothrombin Time; INR: International Normalized Ratio; NSAID: Nonsteroidal Anti-inflammatory Drugs; HF: Heart Failure; AKI: Acute Kidney Injury; ACE: Angiotensin Converting Enzyme; TdP: Torsade de Pointes.

Table 15: Most frequently identified type C interactions.

Interaction	*N*	Mechanism of interaction	Severity	Proposed action and recommendation	Clinical implication
Aspirin + clopidogrel	18	PD	Moderate	**- Monitor therapy.** - Monitor the patient closely for any unusual bleeding or bruising, or signs and symptoms of bleeding such as dizziness; lightheadedness; red or black, tarry stools; coughing up or vomiting fresh or dried blood; severe headache; and weakness. - Monitor INR.	Bleeding.
Aspirin + furosemide	17	PD	Moderate	**- Monitor therapy.** - Monitor patient for decreased therapeutic effect of loop diuretic and alteration in fluid balance (edema). - Monitor patient for salicylate toxicity.	- Diminish therapeutic effect of furosemide. - Increase serum concentration of aspirin.
Aspirin + enoxaparin	11	PD	Moderate	**- Monitor therapy.** - Monitor the patient closely for any unusual bleeding or bruising, or signs and symptoms of bleeding such as dizziness; lightheadedness; red or black, tarry stools; coughing up or vomiting fresh or dried blood; severe headache; and weakness. - Monitor INR.	Bleeding.
Amiodarone + furosemide	10	PD	Moderate	**- Monitor therapy.** - Monitor blood pressure.	Hypotension.
Atorvastatin + ticagrelor	10	PK	Moderate	**- Monitor therapy.** - Monitor for atorvastatin toxicities (rhabdomyolysis).	Increase serum concentration and toxicity of atorvastatin.
Atorvastatin + carvidilol	9	PK	Moderate	**- Monitor therapy.** - Monitor for atorvastatin toxicities (rhabdomyolysis).	Increase serum concentration and toxicity of atorvastatin.
Aspirin + ramipril	8	PD	Moderate	**- Monitor therapy.** - Monitor blood pressure. - Monitor for acute renal failure.	- Diminish the diuretic effect of ramipril. - Enhance the nephrotoxic effect of ramipril.

Ramipril + furosemide	7	PD	Moderate	**- Monitor therapy.** - Monitor blood pressure. - Monitor for acute renal failure. - Monitor particularly patients at risk for AKI using NSAID. - Correction of volume depletion by diuretic therapy interruption of dose reduction prior to ACE inhibitor initiation dose increases. - Patients with HF using diuretic should initiate ACE inhibitors at very low doses and doses should be increased in small increments.	- Hypotension. - Enhance the nephrotoxic effect of ramipril.
Allopurinol + furosemide	6	PK	Moderate	**- Monitor therapy.** - Monitor patients closely for signs and symptoms of allopurinol hypersensitivity reactions (rash, fever, and eosinophilia).	Enhance toxic effect of allopurinol.
Atorvastatin + spironolactone	6	PD	Moderate	**- Monitor therapy.** - Monitor for enhance reduction in endogenous steroid activity.	Enhance toxic effect of spironolactone.

PD: Pharmacodynamic; PK: Pharmacokinetic; AKI: Acute Kidney Injury; NSAID: Nonsteroidal Anti-inflammatory Drugs; HF: Heart Failure;

ACE: Angiotensin Converting Enzyme.

4. DISCUSSION

Rational drug use is an important scope of clinical pharmacy practice. Clinical pharmacy services are centered on individualized drug therapy and aimed to detect, assets, solve and prevent DDIs. DDIs can prevent the rational prescribing and lead to potential severe events and even death. The occurrence of DDIs among hospitalized patients is an important issue that requires more attention by healthcare practitioners. Suggesting that the patient is also having a chronic disease, this may increase the chance of facing a DDI during the drug therapy. Consequently, if this DDI is not identified; it may result later in therapeutic failure, or adverse drug events of reaction, or decrease even patient's compliance with the therapeutic regimen. It is important to assist the incidence of DDIs in patients with chronic diseases and the clinical practice toward these DDIs.

Almost more than half of hospitalized patients are exposed for DDIs. In previous studies, the incidence of DDIs among hospitalized patients with chronic diseases was considered as high. A 6 months study of DDIs in a teaching hospital in South India, showed that 91% of total 204 prescriptions were associated with DDIs. (Kulkarni, 2013) Mousavi et al., used Lexi-comp and Micromedex Drug-Reax system showed that prevalence of potential DDIs for hospitalized patients was 86.2%. (Mousavi, 2017) Another study of potential DDIs in patients admitted to a tertiary care hospital by Roblek et al., reported that the incidence of DDIs was 66%. (Soherwardi, 2012) Despite the variation in the study design, the source of DDIs information and hospital units, our study also suggested a high percentage of DDIs in hospital siting similar the previous studies. In the present study, 1059 prescriptions were analysed to evaluate the frequency of DDIs in hospitalized patients with chronic diseases. We found that 88.1% of patients hospitalized in cardiology, internal medicine and chest diseases and allergy departments were identified with a DDI during their hospitalization.

In line with the mechanisms in this study, DDIs have been categorized according to Lexi-comp as: Pharmacodynamic, pharmacokinetic, unclear and unknown. The majority of DDIs observed in our study were caused by the pharmacodynamic mechanism and pharmacokinetic mechanism. Pharmacodynamic interactions caused 518 (60.3%) while pharmacokinetic interactions 305 (35.5), unclear 27 (3.1%) and unknown 9 (1%) were responsible for less number of DDIs. Likewise, a recent study in 2018, showed that DDIs in hospitalized patient at cardiac and pulmonary departments were caused by

pharmacodynamic interactions 456 (53.27%) while pharmacokinetic interactions 256 (29.90%) and unknown 73 (8.54%) mechanisms were less frequent. (Ramalingam, 2018) Another study conducted by Chavda et al., also reported that over 423 DDIs, 50.83% are pharmacodynamics interactions while 38.53% were pharmacokinetic interactions. (Chavda, 2015) However, these results are different from another study reported that among the 856 interactions, pharmacokinetic DDIs (42%) were more dominant compared to pharmacodynamic DDIs (24%) and unknown mechanisms (34%). (Kulkarni, 2013) This difference might be referred to the difference in disease characteristics of the patients so the type of administered drugs may differ.

The severity assessment in our study showed that most of the DDIs among all patient's characteristics and diseases were moderate (75.4%) in severity; followed by major (15.6%), minor (7.5) and N/A (1.2%). Similarly, a study in hospitalized patients with chronic cardiac diseases showed that 55% of DDIs were moderate and 45% of DDIs were major. (Murtaza, 2016) Also, a published Indian study indicated that moderate interactions (68.72%) were greatest than major (18.94%) and minor (12.33%). (Biradar S. M., 2016) Conversely, Ramalingam et al. reported that prevalence of DDIs was mainly major in severity. (Ramalingam, 2018) Sankar et al., found that among diabetic patients admitted to the hospital; minor interactions (68%) were most dominant followed by moderate (66%) and severe (20%). (Sankar, 2015) The moderate DDIs may affect the patient's clinical status and whenever it detected therapy should be monitored. This level of severity suggests the need for additional treatment, hospitalization, or even extend the hospitalization length.

DDIs are rated by their risk into X, D, C, B and A. A previous study stated that the common type of DDIs is C interactions (78.6%). (Mousavi, 2017) A similar result was obtained in our study. 577 interactions were reported as type C (67.8 %) in compare to 30 interactions of X (3.5), 110 interactions of D (12.9), 123 interactions of B (14.4%) and 11 interactions of A (1.29%). This type of interaction will not cause serious or fatal outcomes. Risk and benefit ratio should be considered when the use of medications with type C interactions and patient should be monitored appropriately.

In this study, the median age of participant patients was 70 years. Patients in the age range between 65-84 years were constituted the highest number of the patients and showed the highest number of DDIs 71 (59.7%) among the total 119 interactions. Younger patients and patients aged 85 and more showed less DDIs [Table 8]. This trend is similar to several studies. A study conducted by Ramalingam et al., showed that majority of potential DDIs in cardiac and pulmonary hospitalized patients were higher approximately in a similar range of age (60–70 years). (Ramalingam, 2018) Also, in another study most DDIs were experienced in a mean age of (64.8 ±9.7). Nevertheless, no statistically significance has been obtained between the age and number of DDIs in our study. A recent study of potential DDIs in hospitalized patients also showed similar result. (Mousavi, 2017) However, several comparable studies have been showed a significant association between DDIs and older patient's age. Ismail et al, founded that patient age 60 years and more is significantly associated with DDIs. (Ismail, 2013) Comparable results may be explained by the differences in sample size and patient's characteristics and diseases.

According to the gender in our study, male patients had higher number of DDIs (70) compared to female patients (49). Another study of DDIs in hospitalized patients at pulmonary department showed similar results. However there was no statistical significance differences were found between both gender and length of hospitalisation with DDIs in this study. Studies by Mousavi et al., Murtaza et al., and Nobili et al. were agreed with our finding. (Mousavi, 2017) (Murtaza, 2016) (Nobili, 2009) Various studies have found different results. Significant association have been founded between male patients and DDIs in cardiac patients. (Ismail, 2013) In addition, Cruciol-Souza and Thomson demonstrated that female patients had a significant association with DDIs. (Cruciol-Souza, 2006)

Many studies have been showed that occurrence of DDIs was increased with length of hospital stay due to increased number of drugs with the increased hospitalization days. a study of Ismail et al. revealed that hospitalization for 6 and more days significantly increase the chance for DDIs. (Ismail, 2013) Moura et al. studied potential DDI in public hospital in Brazil demonstrated that longer the hospital stay increase the likelihood for DDIs. (Moura, 2009) Murtaza et al. also reported a similar association. (Murtaza, 2016) This study contrasts the other studies. We found that DDIs are most frequent for patients stays for 1-2 days (87 interactions) compared to longer days of hospital stay; 3-7 (25.2%)

and more than 7 days (10.4%). This finding explained by the use of multiple medications to treat the acute health problems that resulted in the hospital admission. (Olmos, 2012) Usually, changing in the patient status from outpatient to inpatient may be combined with higher frequency of DDIs. (Himmel, 1996) A study designed to evaluate the prevalence of polypharmacy in hospitalized patients showed that the number of medications is significantly increased with hospitalization. While DDIs were decreased with extended hospital stay days due to the role of healthcare providers in detecting and solving DDIs. Melo et al. showed that exposure to potential DDIs was significantly reduced in patients administered to a hospital department that has a clinical pharmacist. (Melo, 2016) However, in addition to Mousavi and associates, our study showed that no significant difference between the length of hospital stay and DDIs.

Of interest the present study showed a significant positive correlation between the number of DDIs and the number of administered medications [Table 16] Majority of DDIs were encountered with the use of 5-10 medications. As also observed by Doan et al., 80% of patients taking more than 5 drugs were presented with DDIs. (Doan, 2013) Another study showed that increased number of medications from 2 to 7 increased occurrence of DDIs from 13% to 82%. (Goldberg, 1996) The differences of range of medications were due to the differences in methodology and included population in each study. The reason for this significant relation was the presence of polypharmacy. Increased number of prescribed drugs led to increased probability for polypharmacy. (Chavda, 2015) Commonly, more than 5 medications are considered as polypharmacy. (Masnoon, 2017) Patients exposed to polypharmacy should be identified and monitored more closely to prevent unwanted outcomes caused by DDIs. (Bjerrum, 2008)

Table 16: Correlation between the number of prescribed drugs and the frequency of occurred drug-drug interactions.

		Administered drugs	Number of DDIs
Administered drugs	Pearson Correlation	1	.831**
	Sig. (2-tailed)		.000
	N	135	135
Number of DDIs	Pearson Correlation	.831**	1
	Sig. (2-tailed)	.000	
	N	135	135

**. Correlation is significant at the 0.01 level (2-tailed).
DDI: Drug-drug interactions

This study involved patients admitted to cardiology, internal medicine and chest diseases and allergy department. Included patients had at least one chronic condition of cardiac diseases, diabetes mellitus, asthma and COPD. Most of patients were having chronic cardiac diseases (50.2%). [Table 3] Our finding showed that DDIs are most frequent in patients with chronic cardiac diseases (52.3%) followed by other chronic diseases (22.3%), diabetes mellitus (40%), COPD (4.7%) and asthma (1.4%). Patients with hypertension showed greatest frequency of DDIs (82 DDIs) compared to other chronic cardiac conditions. Based on the finding that cardiac diseases were the found in most of the included patients; so there is a chance of increased DDIs in those patients. In general, chronic cardiac diseases composed a major part of all morbidities and mortalities worldwide. (Gupta, 2005) More reasons for higher rate of DDIs among chronic cardiac patients are elder age, multiple drug therapy, and pharmacokinetic or pharmacodynamics nature of the drugs in cardiology. (Faulx, 2008) Hypertensive patient are susceptible for DDIs due some factors as advanced age, gender, increasing number of medications, increasing length of hospital stay, and the influence of heart disease on drug metabolism. (Patel V. K., 2011) Among all chronic conditions, moderate and type C DDIs were dominant; except for diabetic patients. Type B interactions composed the most number of DDIs in diabetic patients. Pharmacological agents administered in those patients usually not tend to cause serious interaction. (Sankar, 2015) Kulkarni et al. had assessed the DDIs according to organ system disorders; found that DDIs in prescriptions of cardiovascular diseases (33%) were higher than DDIs in respiratory disease. (Kulkarni, 2013) Another study showed that most DDIs were encountered in cardiac patients (856 DDIs) whereas pulmonary patients had 675 interactions. Thought a study of pulmonary patients, number of DDIs in patients with COPD (128) exceeded the number in asthma patients (52). (Kameswaran, 2017) Snakar and associates, showed a higher percentage of DDIs in diabetic patients. (Sankar, 2015) This variation resulted from differences in the sample size of diabetic patients among the previous study and this study. However, there was no significant association between the chronic condition and number of DDIs in our study.

In this study, the most frequent DDI being occurred during hospitalization was the combination of clopidogrel with pantoprazole (n=19). This DDI also was considered as the top interaction among D interactions which suggested a therapy modification. Pantoprazole inhibits CYP19 which responsible for the metabolism of clopidogrel to its active metabolite. Therefore, the effect of clopidogrel may be impaired.

The most frequent DDIs causing type X interaction in our study were cefuroxime + pantoprazole (n=3) and Ipratropium/salbutamol + carvedilol (n=3). The pharmacokinetic nature of pantoprazole reduces the gastric acidity and so on reduce the absorption of cefuroxime. Thus, this combination should be avoided. The concomitant use of B-blocker (carvedilol) with B2-agonist (salbutamol) will decrease the bronchodilatory effect of salbutamol by antagonizing the pharmacological effect of B2-agonist. This interaction should be avoided.

Type C interactions were the most important DDIs in our study because it mostly experienced by the patients. Among this type, aspirin + clopidogrel combination showed the greatest number of DDIs (n=18); followed by aspirin + furosemide (n=17) and aspirin + enoxaparine (n=11). [Table 12] Several studies had a quite similar patient characteristics to this study and reported similar results. A study in hospitalized patients with cardiac disease, showed that among the top 10 potential DDIs aspirin + clopidogrel (n=489) and aspirin + furosemide (n=146) similar to our study. (Murtaza, 2016) Another study in diabetic inpatients reported aspirin + enoxaparin interacting pair as a serious interaction founded in the prescriptions. (Sankar, 2015) Mousavi et al. studied the most frequent major and moderate interactions in hospitalized patients; showed that 33 DDIs were aspirin + clopidogrel and 28 were aspirin + enoxaparine. (Mousavi, 2017) Kameswaran et al. identified the common DDIs in cardiology department. As in our study, Kameswaran et al. reported aspirin + clopidogrel, atorvastatin + clopidogrel, aspirin + enalapril and enalaprin + furosemide. While in our study ramipril have been reported instead of enalapril. (Kameswaran, 2017) In our study, the frequencies were much lower than other studies might be due to the differences in number of patients involved and hospital departments. Aspirin and clopidogrel shows a pharmacodynamic interaction. Both medications possess the potential for bleeding and their co-administration increase the risk of bleeding. Addition of aspirin to clopidogrel increases the risk of a life-threatening bleeding in compare to the risk of bleeding of using clopidogrel alone. (Diener, 2004) This interaction is major in severity and patient should be monitored. Awareness of the most frequently DDIs which occurred in our study will decrease the possible risk of these interactions.

However, the use of these drugs in such combination is sometimes required despite the presence of interaction. Therefore, patients should be monitored closely.

In the aspect of duration in which the drug has been prescribed, drugs were categorized to drugs for chronic use and drugs for acute use. Drugs prescribed for chronic use significantly associated with the number of DDIs ($p<0.05$). A higher number of DDIs have occurred with the use of these medications in compare to drugs prescribed for acute use [Table 17]. The number of medications prescribed for chronic conditions is usually higher than the number of medications prescribed for acute treatment especially for patients with multiple co-existing chronic conditions. Also, drugs in the chronic conditions are used for a long time. Therefore, these drugs have high tendency to interact with other drugs. Even though these medications have been prescribed based on the clinical practice guidelines it may have a clinical significant DDIs. (Tso, 2017) As drugs used for chronic diseases therapy will be used for long-life, their interactions may exist in the patient for a long time. Based on this, awareness should be accounted for both types of medications and frequent monitoring for the positive and negative effect of the chronically used drugs should highly be considered by healthcare providers.

Table 17: The frequency of drug-drug interactions with drugs for chronic and acute use.

Type of drug	DDIs N(%)
Drugs for chronic use	**507 (72)***
Drugs for acute use	106 (28)

DDI: Drug-drug interactions

p value <0.05 compared with drugs for acute use

This study is the first study that evaluates the frequency of DDIs in hospitalized patients with chronic diseases in Northern Cyprus. Beside this, our study used Lexi-interact tool of Lexi-comp in the screening of DDIs which have high scores on scope and completeness compared the other DDIs resources usually used in Near East Hospital. Furthermore, this study is the first kind that assets the DDIs among drugs for chronically used drugs and acutely used drugs.

Limitations of the study

There were several limitations in this study. This study was conducted for a short period of time and the frequency of DDIs in patients with chronic diseases needs more time to be evaluated. Also, the number of patients included in this study is limited because the study was carried in one hospital only; thus cannot represents completely Northern Cyprus. In addition, as our study was conducted at a single hospital at Northern Cyprus; the results may not fully represent other hospitals. As a consequence, the generalizability of the results is limited and more studies with larger number of patients and institutions are required.

Moreover, this study lacks intervention component and the actual outcome of the DDIs because of the use of retrospective design. Finally, our study included only specific chronic conditions; further studies are needed to evaluate the incidence of DDIs in more wide range of chronic diseases.

5. CONCLUSION

Drug-drug interactions are common among patients with chronic diseases. The findings of this study showed the most of the DDIs in this population are moderate in severity and reported as X in their risk. Patients with chronic cardiac diseases had a high frequency of DDIs among. The only factor had a correlation to the number of DDIs was number of administered drugs. Drugs used chronically are most likely to cause DDIs.

Improving the knowledge and awareness by healthcare providers of commonly occurring DDIs are measures to minimize the occurrence of DDIs. Physicians should have adequate information of the pharmacological and pharmacokinetic bases for the mostly repeated drugs in the common DDIs combinations. Clinical pharmacist should take responsibility for ensuring the rational drug use by detecting, assessing, solving and preventing DDIs. Well evaluated sources of DDIs should be used for the information.

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7. APPENDIX

7.1. Data collection form

A. Demographics		
Patient number #:	Date of admission:	Date of review:
Age:	Gender:	Unit:

B. Patient history	
Current diagnosis:	Past medical history:

C. Medications history		
Number of medication	Generic name	Pharmacological class

D. Drug-Drug interaction						
Is there at least one drug-drug interaction? Yes ☐ No ☐						
	Drug A	Drug B	Mechanism	Severity	Proposed action	Clinical implication
1						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
2						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
3						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
4						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
5						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
6						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
7						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
8						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
9						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
10						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
11						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
12						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
13						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
14						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
15						
	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				