Prevalence and Predictors of Drug-Related Hospitalizations in Multicenter Study Settings, Addis Ababa, Ethiopia: A Prospective Observational Study

BY: Mulate Belete

A Thesis Paper Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Science, Addis Ababa University in Partial Fulfillment for the Requirements of the Degree of Master of Pharmacy in Pharmacy Practice

May, 2021

Addis Ababa, Ethiopia

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School of Graduate Studies

This is to certify that the thesis prepared by Mulate Belete, entitled with "***Prevalence and Predictors of Drug Related Hospitalizations in Multicenter Study Settings, Addis Ababa, Ethiopia: A Prospective Observational Study***" and submitted in partial fulfillment of the requirements for Degree of Master of Sciences in Pharmacy Practice complies with the regulation of the university and meets the accepted standards with respect to originality and quality.

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Acronyms

AOR	Adjusted Odds Ratio
ADEs	Adverse drug events
ADR	Adverse Drug Reaction
ADWEs	Adverse drug withdrawal events
ACEIs	Angiotensin Converting Enzyme Inhibitors
DRHs	Drug-Related Hospitalizations
DRHA	Drug-Related Hospital Admission
DRP	Drug related problem
EW	Emergency Ward
FDA	Food and Drug Administration
MRPS	Medicine-Related Problems
OR	Odds Ratios
SD	Standard deviation
SPSS	Stastical Package for Social Science
TASH	Tikur Anbessa Specialized Hospital
TFs	Therapeutic failures
WHO	World Health Organization
Y12HMC	Yekatit 12 Hospital Medical College
ZMH	Zewditu Memorial Hospital

Abstract

Background: Drug related hospitalizations (DRHs) represent a substantial burden on health care resources worldwide and are considered as one of the leading causes of morbidity. Studies carried out in various countries, the extent of DRHs has been estimated to be between 16% to 41.3%.Of those, more than half of the cases were preventable. Whereas in Ethiopia the prevalence and factors independently associated with DRHs are not known. Therefore, the aim of this study was to determine the prevalence and predictors of DRHs in emergency ward of Tikur Anbessa Specialized Hospital, Zewditu Memorial Hospital and Yekatit 12 Hospital Medical College, Addis Ababa, Ethiopia.

Methods: A prospective observational study was conducted from August to September, 2020 in the three selected hospitals. Participants were interviewed and their medical charts were reviewed through a structured data collection format. DRHs were assessed using Helper's and strand's drug therapy problems classification system. The data were entered and analyzed using Statistical Package for Social Science (SPSS) version 26.Descriptive statistics and binary logistic regressions were performed. P-value <0.05 in multiple binary logistic regression was taken as significant level and results were presented in texts, tables and charts.

Result: The numbers of recruited and screened patients were 2655.Out of them, 423 participants who fulfilled the inclusion criteria were enrolled in the study. Of those who met the inclusion criteria, more than half of them (216, 51.1%) were females. The mean age (SD) of the study participants was 47.50 (±17.21) years. The mean length of hospital stay (SD) was 10.29(±8.99) days and ranges from 2 to 96 days. Among the included study participants, near to three fifth (245, 57.9%) of patients were hospitalized due to drug related problems, of which 87.8% were deemed preventable. Of those, more than half (130, 53%) of them experienced failure to receive drugs followed by untreated indications (94, 37.8%). The main reasons for failure to receive drugs were due to patients preferred not to take the medications (43, 33.1%), they feared adverse events (18, 13.8%) ,drug products were not available (17, 13.1%), patients felt better (17,13.1%) and cost of medications was too expensive (16,12.3%).*Factors associated with DRHs were old age (age > 64 years (Adjusted Odds Ratio [AOR] = 7.451, 95%CI: 1.889-29.397), tertiary educational level (AOR=0.360, 95%CI: 0.141-0.923), participants who did not have any occupation (AOR=3.409, 95%CI: 1.120-10.374),students (AOR=*6.331,95%CI:1.375-29.153) *presence of co-morbid diseases (AOR=2.004,95%CI: 1.095-3.668), and hospital stay > seven days (AOR=2.186, 95%CI: 1.412-3.382).*

Conclusion: DRHs were common among emergency ward patients in the study settings. More than four fifth of DRHs were deemed to be preventable.

Key words: Drugs related problems, Drug related hospitalization, Predictors, Prevalence, Ethiopia.

1. Introduction

1.1. Background

Drugs can be ordered for the intention of attaining specific outcomes that improve the patient's quality of life. These outcomes include curing of a disease, reducing or eliminating of symptoms, arresting or slowing of a disease process, and preventing a disease. More or less, the patient benefits from administered medications(Robert J. Cipolle, 2012, STRAND, 1990).However, at any time drugs are given, any number of outcomes ranging from minor disease signs and symptoms to death which diminish the patient's quality of life can occur. These under optimal outcomes can result from drug related problems (DRPs). Any deviation from the intended beneficial effect of a medication can elicit DRPs (Johnson and Boatman, 1996). DRP was defined according to Helper and strand as 'an undesired event or circumstance due to drug therapy that actually or potentially interferes with desired health outcomes'. They are followed by drug related morbidities which are characterized by symptoms and signs of diseases owing to medications misuse. One or more DRPs may develop in a given patient after the initiation of drug therapy. They can be associated with significant morbidity and mortality (STRAND, 1990, Al Hamid et al., 2014, Alayed et al., 2019, Andreazza et al., 2011).

In the globe, medications use has been becoming increased because of the presence of large number of diseases which in turn contributed to the production of medications in advances from pharmaceutical industries. Therefore, advances in drug therapies led to an apparent increase in the incidence of DRPs leading hospitalization. Hospitalization can be defined as drug related if it is directly related to one of eight predefined Helper and Strand classifications of DRPs: adverse drug reaction(ADR), drug interaction, improper drug selection, untreated indication, sub-therapeutic dosage, supra-therapeutic dosage, failure to receive drugs, and drug use without indication (Gustafsson et al., 2016, Kanagaratnam et al., 2016, Lea et al., 2019, Pattanaik et al., 2009, Pellegrin et al., 2017, Peter J. Zed, 2015, R L Howard, 2003, Singh et al., 2011, Yosef H. Al-Olah, 2008, STRAND, 1990).

The use of medicines can cause unwanted outcomes to the patients in several ways. One means, ADRs can be incurred even when a medicine is prescribed aptly and used correctly, and may arise if the patient has been taking the medicine long-term, e.g. angioedema secondary to drugs like enalapril. According to the World Health Organization (WHO), an ADR is any harmful, undesired and inadvertent drug effect that occurs at doses used in human for therapy, diagnosis or prophylaxis(WHO, 1969).Other way, it may arise due to errors involving prescribing (including inappropriate or over-treatment, and failure to prescribe the indicated treatment or under-treatment), dispensing, administering, reconciling, or monitoring of medicines. Lastly, undesired events of drug therapy may also occur from poor adherence (incorrect or non-use by the patient, which may be intentional or non-intentional) (Centre, Feburary,2015, Alayed et al., 2019).

Drug related hospitalizations (DRHs) negative burden are significantly evident especially in adult and elderly patient's life career. As it is implicated in a systematic review done in 2019, the prevalence of DRHs ranges from 1.3% to 41.3%.Of those, more than 70% were accepted to be preventable (Ayalew et al., 2019). As stated in various international studies, more than 50% of DRHs could be preventable (Al Hamid et al., 2014, Gustafsson et al., 2016, Hasford, 2011, Kanagaratnam et al., 2016, Kent M. Nelson, 1996, Nivya et al., 2015, Pellegrin et al., 2017).

DRPs resulting DRHs were defined as preventable if the patient failed to take a drug that is known to reduce or prevent the symptoms according to the prescribed directions, took a drug for which a patient had a known allergy, drug treatment was obviously improper, dosage differed from accepted recommendations, took a drug that was not indicated, and if there was a failure to monitor by a physician at reasonable time intervals and inadequate monitoring due to inability to see a physician e.g., financial difficulties whilst if there were no reasonable actions to prevent DRPs which termed as non-preventable (Almut G Winterstein, 2002, Kent M. Nelson, 1996).

1.2. Statement of the problem

Over the past decades, DRHs have been stated as prevailing. In the United States, 17 million emergency ward (EW) visits and 8.7 million hospital admissions accounted from DRPs annually(Mohamed Al-Arifi and Aljadhey, 2013, Johnson and Boatman, 1996).And, one million patients were hospitalized in the United States in 1971 because of ADRs and 15,000 hospitalizations due to ADRs were reported to the Food and Drug Administration (FDA) in 1987(STRAND, 1990).Drug-related visits to the ED represent a considerable problem that put in to the overall pressure on health care system. It has harmful consequences on patients and societies. It increases morbidity and mortality rates, health care cost, decreases income and household productivity and reduced quality of life (Centre, Feburary,2015, J. HALLAS, 1990, Alayed et al., 2019, Andreazza et al., 2011, Dammalapati et al., 2018).

The studies carried out in different study areas of the globe manifested the extent of DRHs have been estimated to be between 16% to 41.3%.Of those, 50% to 95% were accepted to be preventable. Among DRHs, supratherapeutic dosage (10.3%-12.7%), non-compliance (10.6%-65.8%), ADRs (10.7%-45.5%) and untreated indications (10.7-13.3% were identified (Dammalapati et al., 2018, Gustafsson et al., 2016, Kent M. Nelson, 1996, Leslie Jo Samoy, 2006, Mohamed Al-Arifi and Aljadhey, 2013, Pellegrin et al., 2017).

Hospitalizations due to DRPs are likely to increase as people live longer, have greater numbers of chronic conditions, and take more medications. Among adults 65 years of age or older, 40% take 5 to 9 medications and 18% take 10 or more. It was associated with age-related receptor down regulation, metabolizing and excreting organs physiological functions change, numbers of coexisting conditions, and polypharmacy have been associated with an increased risk of adverse events and older adults are nearly seven times as likely as younger persons to have adverse drug events that require hospitalization(Daniel S. Budnitz, 2011).

Published studies reported DRPs as a frequent cause of visits to an emergency ward (EW) and hospitalization and which sequentially predisposed the patient to economical, psychological and social crisis. DRHs have been more common in developing countries. If preventable DRHs occurred in those countries, significant economical, social and psychological and physical catastrophes might be introduced to patients, care givers, health institutions, drugs and countries at large. For instance, patients might be rendered to numerous expenses including diagnosis, admission and treatment costs in addition to productivity loss. Therefore, economical burden is so huge and patient's social interaction in different common events was negatively affected. Patients will manifest variety psychological disorders. For instance , 2.3% had depression in this finding (Citrome et al., 2019). Furthermore, patients may contract physical disability and even death. Study conducted in Canada; twenty-three patients (30%) had a nonpermanent disability, such as severe dehydration and abdominal pain due to Clostridium difficile diarrhea and severe pain after a fall that resulted in rib fractures. Two patients (3%) had permanent disabilities(Forster; Harvey J. Murff, 2003). Health institutions services are also greatly affected with preventable DRHs. Another problem that might be occurred in patients having DRHs required many numbers of medications than they require before DRHs occurred. Moreover, this can render greater consumption of medications and thereby other DRPs like drug interactions are presented. For example patients having hypertension can be treated with one drug but if remained untreated, stroke might be developed and treated with multiple therapies. These illustrations were supported with the following articles(Daniel S. Budnitz, 2011, Karuppannan et al., 2013, Kent M. Nelson, 1996, Leslie Jo Samoy, 2006, Pellegrin et al., 2017)and if DRPs left untreated, drug-related morbidity may eventually result in drug related mortality(STRAND, 1990).Studies reported that around 90% of DRHs were preventable (Dammalapati et al., 2018, STRAND, 1990).

1.3. Significance of the study

Data on the prevalence and predictors of DRHs are scarce in developing countries. As far as our knowledge is concerned, there are no studies about DRHs in Ethiopia. Therefore, this study explored the extent of DRHs and revealed categories of DRHs and also the predictors that favored the occurrence of DRHs. This will serve as a starting point for future evaluation of the impact of DRHs for studies in different study areas of Ethiopia. Findings from this study would also initiate health facility managers and professionals to culminate patient's hospitalization due to DRPs.

1.4. Literature Review

1.4.1. Prevalence and categories of drug related hospitalizations

Several studies have previously investigated the prevalence and risk factors for DRHs in various patients' population (Andreazza et al., 2011, Daniel S. Budnitz, 2011, Gustafsson et al., 2016, Lea et al., 2019, Marcum et al., 2012).

Study done in Texas, America; drug related hospital admission (DRHA) was occurred in seventy three (452, 16.2%) patients. Of those, forty patients (54.8%) had therapy failure, (24, 32.9%) experienced an adverse reaction, and the remaining patients were admitted due to overdoses. Among those,49.3% of their admissions were definitely preventable (Kent M. Nelson, 1996).Study undergone in Canada, the occurrence of DRHs among admissions was (136,24.1%), of which 72.1% were preventable and the most common categories of DRHs were ADRs (35.3%, improper drug selection (17.6%), and noncompliance (16.2%)(Leslie Jo Samoy, 2006).Another study carried out at America in 2011 showed that more than two third of patients who visited ED were hospitalized for Adverse drug events (ADEs). Amid these, nearly two third of them were due to unintentional overdoses(Daniel S. Budnitz, 2011).As Marcum et al. finding, the incidence of DRHA was (40, 5.9%).It was resulted from thirty-four therapeutic failures (TFs) and eight adverse drug withdrawal events (ADWEs).Of these admissions, 90.0% were considered as potentially preventable because it was mostly attributed to medication non adherence and prescribing errors(Marcum et al., 2012).Study done in Hawaii province of America, medication related readmissions were also observed in 26% readmission patients and all of them were preventable. The most common DRHA categories were failure to receive drugs due to patient choice (23.8%), untreated condition for which medication is indicated (13.3%), supratherapeutic dose (10.5%), and subtherapeutic dose (10.5%) (Pellegrin et al., 2017).

Study done in Brazil showed that the frequency of DRPs leading to emergency ward visit was (350, 31.6%) and the most frequent DRPs leading hospitalizations were ineffectiveness and ADRs. Ineffectiveness was mainly related to inadequate dosage regimens (17.9%) and refractoriness (12.2%). ADRs and non-adherence were also identified in28.5% and 17.1% of DRHs patients respectively (Andreazza et al., 2011).Furthermore ,a cluster randomized

controlled trial carried out at European multicentre showed that overprescribing and under prescribing, as well as non-adherence with drug regimens has been linked with DRHs (Luise Adam et al., 2019).

Study done in Denmark, 10.8% of all admissions was related to be drug-related. Of these, 8.1% were admitted due to ADRs and 2.7% were TFs due to ineffective dosage (J. HALLAS, 1990).Another finding in United Kingdom, of the admissions, (265, 6.5%) were determined to be drug related and 67% of those were judged to be preventable. The admissions were mainly associated to problems with prescribing (63 ,35%), monitoring (46,26%), and adherence to medication (53,30%) (R L Howard, 2003).Other articles in Sewdin and Greece, the prevalence of DRHs were comparable (41.3 %, 45.5 %, respectively). An ADR was the most common causes DRHs (Alexopoulou et al., 2008, Gustafsson et al., 2016).Dosage too high (12.7 %) and noncompliance(10.6 %) were also frequently encountered DRPs resulting DRHs followed by ineffective/inappropriate drug use and interactions accounted for 10.6 and 6.9% respectively (Gustafsson et al., 2016). Whereas study done in Norway revealed that 38% of hospitalizations were due to drug-related in 155 of the 404 included patients (Lea et al., 2019).ADR and nonadherence were the most types that have been found for DRHs (Lea et al., 2019).

Study undergone at India in 2011 and 2018, 3.5% and 17.2 %patients were admitted due to DRHAs respectively (Dammalapati et al., 2018, Singh et al., 2011).The most common DRHs was due to non-compliance (50.5%) and ADRs (39.11%)(Dammalapati et al., 2018).In study done in India at 2011,the most common DRP was noncompliance (55, 46.6%)(Singh et al., 2011).Another study conducted in India proved that out of 1833 admissions, 5.01% were due to DRPs. Non compliance (66%) followed by ADR (28%) and drug overdose(6%) were accounted for DRHs. The most common reasons for noncompliance in this study were inadequate knowledge about the disease, poor understanding of the need for regular medication followed by forgetfulness. As the Authors confirmed that noncompliance was due to the misconception that once diseases like blood pressure, blood sugar, seizures, etc. are under control there is no need to continue the medications. Another reason could be inappropriate communication between the patient and attending physician (Pattanaik et al., 2009).

Study in Saudi Arabia, of 557 patients admitted through the ED during the study period, 14.7% were due to DRPs. The most common classifications of DRPs admission were due to failure to receive medications (47.2%),followed by ADRs (24.5%) and drug overdose (11.3%(Yosef H. Al-Olah, 2008).Additionally, of 300 patients, 18.7% were presented to ED due to DRPs.The most common DRPs was due to ADRs (30.4%) and non-compliance(30.4%), followed by untreated indication (10.7%), then drug interactions ; supratherapeutic and subtherapeutic dose (7.1%for each)(Mohamed Al-Arifi and Aljadhey, 2013).A systematic review done in Saudi Arabia, in all reviewed studies, hospitalization due to drugs had a high prevalence, in the range of 4.6–12.1%(Al Hamid et al., 2014).ADR and noncompliance were the main causes leading to hospitalization. Additional causes included the following: treatment ineffectiveness, under treatment and inadequate instructions, insufficient laboratory test monitoring , drug–drug interaction and toxicity(Al Hamid et al., 2014).Study done in Saudi particularly on ADRs, out of 4739 admissions to the wards, (38 ,0.801%) was related to an ADR(Alayed et al., 2019).

Study done in Malaysia showed that the frequency of DRHs was 39% .Of those 79% were due to TF, 21% were due to ADR, 5% were due to dose to high, and 3% were due to medication error(Karuppannan et al., 2013) and the recent systematic review depicted that the prevalence of drug related hospital admission(DRHA) varies from 1.3% to 41.3% with the average rate of 15.4%. About one third of drug related hospital admissions were definitely preventable and more than 40% were also potentially preventable (Ayalew et al., 2019).

1.4.2. Medications and diseases involved in drug related hospitalizations

Study conducted in America, hematologic agents, endocrine agents, cardiovascular agents, central nervous system agents, and anti-infective agents were the five most common therapeutic categories implicated; accounting for an estimated 88.3% of hospitalizations due to DRPs with four most commonly implicated drugs. They were warfarin (33.3%), insulins (13.9%),oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%) accounted for an estimated two thirds of hospitalizations(Daniel S. Budnitz, 2011).Another finding in Texas, America demonstrated that drugs that were involved in DRHs were hypoglycemics(15.8%), diuretics(13.2%),and cardiovascular agents (10.5%) (Kent M. Nelson, 1996). Another finding revealed that antiplatelets, antiepileptics, hypoglycaemics, diuretics, inhaled corticosteroids, cardiac glycosides and beta-blockers were most commonly associated drugs with the preventable drug related admissions(R L Howard, 2003).

Marcum et al. founded that the most common disease related with DRHs were heart failure exacerbations (8,20%), coronary heart disease symptoms (n = 6), tachyarrhythmia (n = 3), and chronic obstructive pulmonary disease exacerbations (n = 3)(Marcum et al., 2012) and in other study at Canada, the most common drug classes associated with DRHs were cardiovascular agents (27.5%), antibiotics (23.4%),central nervous system agents (7.8%),anticoagulants (5.4%), and hypoglycemic agents (4.8%) with a specific drugs of aspirin(14.0%), furosemide (7.4%), ciprofloxacin (7.4%), warfarin (6.6%), ramipril (6.6%), and spironolactone (5.9%)(Leslie Jo Samoy, 2006).

Study in Sewdin, 264 drugs were judged to be involved in 189 drug related admissions, of which cardiovascular (29.5 %) and psychotropic (26.9 %) drugs were the most commonly involved drug classes (Gustafsson et al., 2016).

Of the 71drug categories participated in DRHs, the most frequently involved were those acting on the cardiovascular system (24.3%) and on the nervous system (18.6%) and over-the-counter drugs (13%) (Andreazza et al., 2011).In Greece, the drugs most often involved in DRHs were non-steroid anti-inflammatory drugs (NSAIDs), followed by diuretics, aspirin, oral anticoagulants, and oral hypoglycemic agents (Alexopoulou et al., 2008).But at India,

cardiovascular drugs followed by oral hypoglycemic drugs were associated with DRHs (Dammalapati et al., 2018).Another study done at India, most common drugs associated with definite DRPs were oral hypoglycemic, antihypertensive, chemotherapy (especially antiretroviral agents) and insulin (Singh et al., 2011). The common diseases associated with DRHs in India were cerebrovascular accident (19.44%), followed by accelerated hypertension (18.36%) and diabetic ketoacidosis (14.04%) (Pattanaik et al., 2009).

As systematic review done in Saudi Arabia showed, most DRHs encountered were prevalent among adult patients taking medicines for cardiovascular diseases and diabetes(Al Hamid et al., 2014). Another study that was carried out in Saudi Arabia, the most common drug groups associated with DRPs leading hospitalization were antihypertensive agents (21.5%), anticoagulants (14.3%), immunosuppressants (12.5%) and chemotherapeutic agents (10.7%). The most common diagnosises associated with DRHs were hypertension (8.9%), diabetes mellitus (8.9%), stroke (7.1%), urinary tract infection (5.4%), drug overdose (5.4%), and febrile neutropenia (5.4%) (Roughead et al., 2016).

In Malaysia, cardiovascular drugs (n = 222, 50%), antidiabetics (n=96, 22%), and antiasthmatics (n=65, 15%) were most commonly associated with DRHs. The most common complaint by patients admitted due to a TF was chest pain, whilst hypoglycemia was the main cause of admission related to ADRs (Karuppannan et al., 2013).

1.4.3. Factors associated with drug related hospitalizations

Among predictors that were associated with DRHs, polypharmacy has showed significant correlation (p=0.0018) while duration of hospital stay was significantly longer in the nondrug-related group (median 6 days, range 1-74 days) than the drug-related group (median 4 days, range 1-36 days, p=0.0018).Therefore ,it has illustrated insignificant correlation with DRHs. Age and gender of the patients did not differ significantly between DRHs and non-DRHs groups(Kent M. Nelson, 1996). Finding in Canada described results of the multivariate logistic regression analysis indicate that the occurrence of DRHs was independent of age (p=0.26), sex (0.14), number of prescription drugs prescribed (p=0.22), number of over the counter drugs taken (p=0.82) and, use of complementary and alternative medicine (p=0.89)(Leslie Jo Samoy, 2006).

Study conducted at Brasil revealed that educational level and the numbers of drugs being taken were factors independently influencing the development of DRHs. A high school educational level was a protective factor against the development of DRHs (OR=0.32; CI95%: 0.16–0.64). The use of five or more drugs contributed to the occurrence of DRHs (OR=2.21; CI95%: 1.3–3.9) whereas age showed no correlation with the development of DRPs resulted DRHs (OR=1.14; CI95%: 0.65–2.11) (Andreazza et al., 2011).

Another study done in Sweden, DRHs were more common among people taking more drugs (OR, 1.060 [95 % CI, 1.004–1.119]; P = 0.035) and among younger patients (OR, 0.969 [95 % CI, 0.941-0.997]; P = 0.031) and less common with increasing age (OR, 0.968 [95 % CI, 0.941–0.997]; P =0.028). Gender and living arrangement were not significant differences between patients with and without DRHAs (Gustafsson et al., 2016).

Finding at study in India revealed that statistically significant correlations were found in numbers of prescribed drugs and over the counter drugs used by patients (P-value<0.001 for each) and also in patients who had education below high school had significant correlation with DRHs(P-value<0.05)(Singh et al., 2011).

Another study undergone in India, the factors remarkably identified with DRHAs were age, patients having rural residency, illiterate with low economic status, diabetes mellitus, hypertension and polypharmacy. Of those, co-morbid conditions like hypertension diabetes mellitus and polypharmacy insignificantly($p<0.001$) associated with DRHs(Dammalapati et al., 2018).

Systematic review done in Saudi Arabia, old age and polypharmacy were the main risk factors reported in most studies. The others were co morbidities, impaired cognition, patient's insufficient awareness of health and disease and drug allergy, and females, low education level, cohabitation and immobilization were mentioned as determinants to DRHs(Al Hamid et al., 2014).Another systematic review conducted in 2019 stated that poly pharmacy, old age and female sex were mentioned as determinants for DRHs by a number of studies. Presence of multiple co morbidity, lower educational level, functional dependence, young age and male sex were also mentioned in some studies as factors that influence hospital admission because of DRPs (Ayalew et al., 2019).

2. Objectives

2.1. General objective

The aim of this study was to determine the overall prevalence, categories of drug related hospitalizations and predictors among patients hospitalized through an emergency ward (EW) of Tikur Anbessa Specialized Hospital (TASH), Zewditu Memorial Hospital (ZMH) and Yekatit 12 Hospital Medical College (Y12HMC), Addis Ababa, Ethiopia.

2.2. Specific objectives

- ✓ To determine the overall prevalence of drug related problems hospitalizations at TASH, ZMH and Y12HMC.
- ✓ To identify the most common categories of drug related problems leads to hospitalizations in the three study settings.
- ✓ To identify factors independently associated with drug related hospitalizations among patients hospitalized through the EW of the study settings.

3. Methodology

3.1. Study Settings

The study was carried out in EW of the three hospitals of Addis Ababa city; TASH, ZMH and Y12HMC.TASH was inaugurated in 1972. It has 700 beds and it is a tertiary care teaching hospital of Addis Ababa University. This hospital offers diagnosis and treatment for patients and it trains large number of undergraduate and graduate students. It is also an institution where specialized clinical services like cancer diagnosis and treatment that are not available in other public or private institutions are provided to the whole nation. In TASH, outpatient, inpatient emergency services are delivered. The EW provided services to about or more 13920 patients per year (Yosha et al., 2021). Y12HMC was established in 1923.It is also a tertiary level referral and teaching hospital in Addis Ababa that provides both inpatient and outpatient treatment for a large number of people from the Addis Ababa city and different nation parts. The hospital has total of 3 EW rooms. The adult medical EW is collocated with adult surgical EW. It served around 10560 patients per year in EW. The third hospital where in this study was carried out is ZMH which was built and owned by the Seventh day Adventist Church, but was nationalized during the Derg regime in 1976 and it is one of a teaching and general referral hospital in Ethiopia and it served for about 10560 patients per year at EW.

3.2. Study design and period

A prospective observational study design was used. The data was collected using a structured questionnaire from August to September, 2020.

3.3. Source population

All patients who visited three hospitals of EW were the source of populations.

3.4. Study population

All patients who admitted at EW of the three selected hospitals during the study period and fulfilled the inclusion criteria were recruited.

3.5. Inclusion and exclusion criteria

3.5.1. Inclusion criteria

- ✓ Patients who had medical history with completed data.
- ✓ Age greater than and equal to 14years of age

3.5.2. Exclusion criteria

- ✓ Patients who were refuse to participate.
- ✓ Patients presented with trauma and injuries associated with accidents (e.g. road traffic accidents, beaten by stick, stabbing and bulleting)
- ✓ Patients who were poisoned/intoxicated(for instance snake bite, alcohol intoxication or use of pesticide)

3.6. Sample size determination and techniques

Since there was no study done on DRHs in Ethiopia, the sample size was estimated using the general formula for single population proportion. The sample size was computed as follows.

$n = [(Z\ \alpha/2)^2 \times p\ (1-p)]$ ✓ $d^2 = [(1.96)^2 x 0.5 x 0.5] / 0.05^2$ **=384**

Hence; n = Sample size; Zα/2 = Confidence level at 95% = 1.96, P = Proportion of drug related hospitalization is 50%, d = margin of error of 5%=0.05

The calculated sample size using this formula was 384. Adding 10% contingency and it makes the sample size to be 423 patients. Since this research was being conducted in three hospitals, patients flow per year in all three hospitals EW were 35040.In TASH alone, 13920 patients were served annually as it is mentioned in the section of study settings along with ZMH and Y12HMC EW patients served (10560 for each).Therefore, 423 participants of the final sample size were computed out of the overall three hospitals patients served annually in EW. Accordingly, 169 participants were included from TASH, 127 participants from ZMH and other 127 participants from Y12HMC and convenient sampling technique was used.

3.7. Study variables

3.7.1. Dependent variables

- Drug related hospitalizations (DRHs)

3.7.2. Independent variables

- Socio-demographic characteristics (age, gender, employment, marital status, level of education and residence)
- Clinical characteristics (presence of co morbid condition, number of drugs used before admission, use of traditional medicine and hospital stay)
- Social habits(smoking, alcohol use and physical activity)

3.8. Data collection and management

3.8.1. Data collection instrument

A structured questionnaire check list prepared after reviewing similar articles were used to collect data (see Annexes) (Andreazza et al., 2011, Dammalapati et al., 2018, Gustafsson et al., 2016, Pellegrin et al., 2017). For reasons to DRHs, Helper and Strand DRP category was used(STRAND, 1990).

3.8.2. Data collection approach and interpretation

All the necessary data including the patients demographic details (age,sex,marital status, education level, employment), and clinical information like number of medications being taken prior to admission were collected and documented in data collection tools through interviewing the patients. Furthermore, patient's medical records were reviewed by data collectors to identify clinical information (disease history, allergic status, admission diagnosis, length of hospital stay during admission, number of medications being taken prior to admission, data on laboratory investigations) and supplementary information and clarifications on some patient's medical information were obtained through discussion with the physicians and residents. By applying those data gathering approach, different categories of DRPs resulting hospitalization with their possible causes were determined. Data were collected, using a structured questionnaire, by three

pharmacists, having Master of Science of degree in clinical pharmacy, had basic knowledge on pharmaceutical care services and also received training on how to obtain data from patient's medication charts and on how to approach the patients and health care professionals. They were using updated diseases management guidelines like Ethiopian standard treatment guidelines for Hospitals third edition, 2014 even it has formulated for general hospitals; and references such as Medscape; UpToDate latest version and Micromedex for drug interaction in order to determine the presence of DRPs brought DRHs. Furthermore, latest guidelines generated by American cardiology center, American heart association, European cardiology society, American diabetic association, ,Ethiopian antiretroviral therapy and tuberculosis guidelines ,different protocols for various cancer treatment compiled by TASH oncologists in conjunction with pharmacotherapy text books such as pharmacotherapy a pathophysiologic approach latest edition, applied therapeutics latest edition were being used. Accordingly, pharmacist's therapeutic knowledge along with physicians documentation in patients' medical chart implemented to interpret subtherapeutic and supratherapeutic dosage. Participants hospitalized attributed to failure to receive drugs were decided via using physician's recording documentation, clinical pharmacists knowledge and patients reporting evidence. And also, untreated indication and improper drug selection were being evaluated and interpreted by using guidelines. For instance, if patients presented with cardiac diseases which were untreated or improperly treated, American heart association guidelines, and UpToDate latest version applied to interpret them. To minimize bias, the three pharmacists were evaluated independently following each pharmacist who identified DRPs rendered hospitalizations. Consequently, they were meeting and discussing about their judgment to DRPs resulting DRHs. Accordingly, DRPs rendering DRHs were determined after they have been reaching on concord. Moreover, Physicians and residents were involving in interpreting DRPs causing hospitalizations. Once DRPs resulting DRHs were identified, they were recorded and classified using DRPs registration format according to Helper's and Strand's classification. Upon patients with DRHs were being visited the EW, interventions were made. Interventions like communicating the physicians to initiate of the intended discontinued drugs, bargaining with physician to discontinue improper drug and drugs causing ADR, initiating the preferred medications, reducing supratherapeutic dosage and increasing subtherapeutic dosage. Moreover, numerous counseling tips regarding their drugs use, direction for use and consequences if not discontinued have been delivered to patients who presented with failure to

receive drugs. The data collection process was supervised, and data abstraction formats were reviewed and cheeked for their completeness every day by principal investigator. After data was checked for completeness, it was edited, cleaned, and analyzed.

3.8.3. Data collectors

Data were collected by three pharmacists who have Master of Science in clinical pharmacy and they were being trained on how to collect the necessary data using structured questionnaire by interviewing the patients and reviewing their medical records.

3.8.4. Data quality assurance

To assure the quality of the data, the structured check list was designed and the questionnaire was pre tested on ten patients in TASH to see the soundness of the questionnaire and to make necessary corrections prior to starting the study. Based on the results obtained from pre-test, amendment was made on the assessment tools and way of assessment based on the inputs found on pre-test. The principal investigator was closely supervising the data collection on a daily basis. At the end of each data collection days, the principal investigator checked the completeness of filled questionnaire information to ensure its quality.

3.8.5. Data analysis

The data were entered and analyzed using Statistical Package for Social Science (SPSS) version 26. Mean and standard deviation for continuous variables and frequency and percentage for categorical variables were computed by using descriptive statistics in SPSS to summarize socio-demographic and relevant clinical characteristics of the study participants. Texts, tables and charts were used to present the results. Furthermore, univariate binary and multiple binary logistic regressions were performed to analyze factors that predict drug related hospitalizations. Dependent variables were coded as 0 for non drug related hospitalizations and 1 for drug related hospitalizations in SPSS regression analysis. Independent variables after they appropriately labeled were taken under covariates and went to categorical covariates based on enter method in which reference indicators were provided for each covariate. Finally analysis was under taken and membership for drug related hospitalizations was predicted probability. Variables whose

P-values < 0.2 in the univariate analysis were included in the multiple binary logistic regressions to control the effect of confounders. The level of significance was chosen at p–value ≤ 0.05 and results were reported as odds ratios (OR) with 95% confidence intervals.

3.9. Ethical considerations

Prior to study initiation, letter of ethical approval (Ref No;ERB/SOP/172/08/2020) was obtained from ethical review committee, School of Pharmacy, Addis Ababa University. In addition, permission was obtained from the hospital's medical directors to conduct the study and names was not be used rather codes to maintain confidentiality of the information throughout the study period. Verbal consent from patients was obtained after the provision of information regarding the purpose of the study and its risk for the interviewee which could be time to be spent during the interview (maximum of 30 minutes). Patients were told the reasons of being selected to be included in the study and assured that waning participation would not have any influence on the right to get treatment. Patients were also told about their rights to withdraw from the study at any time.

3.10. Operational definitions

Study terms were defined as follows:

- Drug related hospitalization was patient's visit or admission through EW as a consequent to DRPs which is brought either by administering a particular drug or not.
- Drug use without indication refers that taking of a drug for no medically convincing indication;
- Failure to receive drugs: diseases that resulted from not receiving a drug for unavailability or unaffordability drugs, patients no need to take drugs or stop taking medications upon they felt better e.t.c.
- Improper drug selection: diseases occurred due to taking of ineffective drug or expired drugs;
- Untreated indication: medical condition needing new drug therapy, or preventive therapy is needed to reduce the risk of developing a new condition, or a medical condition requires combination therapy for better efficacy (STRAND, 1990).

- Regular physical activity: A physical exercise that that is performed for at least 30 minutes three times or more per week since walking which include different aerobic exercise like running, jumping a rope, push-up ,set-up and e.t.c.
- Polypharmacy: Greater than or equal to five drugs were concomitantly being taken.
- Comorbid diseases: More than or equal to two diseases were presented in a patient termed as comorbid diseases.

4. Results

4.1. Socio-demographic and clinical characteristics of the study participants

From 2655 participants enrolled in this study, a total of 423 study participants were included for analysis. Of them, 169 participants from TASH, 127 from ZMH and another127 from Y12HMC were included (***Figure 1***).

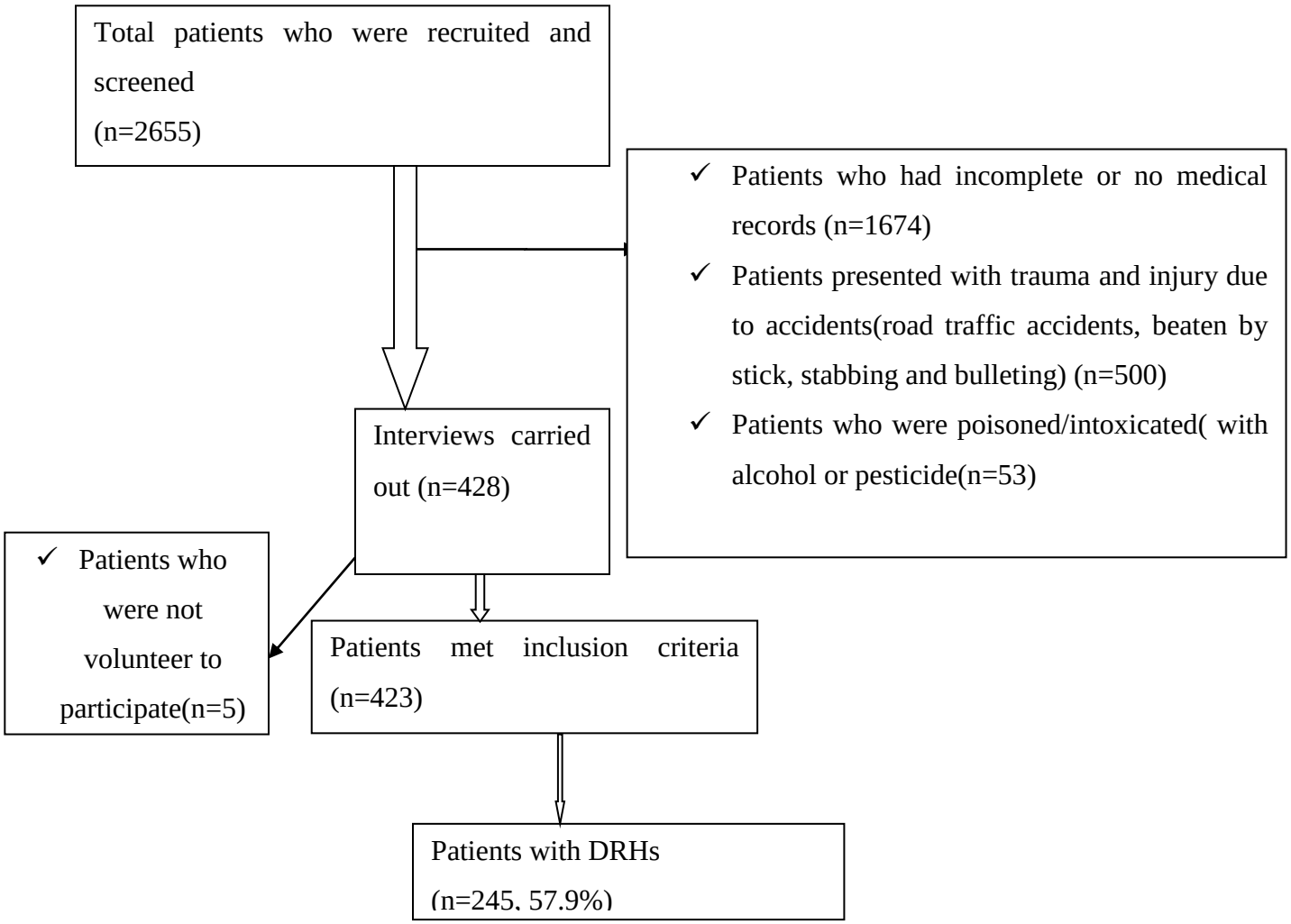

Figure 1: *Patient's inclusion information flow chart in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 423)*

As socio-demographic and clinical characteristics of the participants depicted in *Table 1*.More than half of the participants (216, 51.1%) were females. The mean (SD) age of the participants was 47.5 (±17.21) years and nearly two third (275, 65%) of the patients were age greater than or equal to 40 years. More than 70 % (301, 71.1%) of the total participants' level of education was below secondary school. More than half (223, 52.7%) of the included patients whose employments have been retired (97, 22.9%), laborers (83, 19.6%) and lived dependently with others (43, 10.2%).Nearly three fourth of them (304, 71.9%) resided in Addis Ababa and majority (322, 76.1%) of the participants were follow Orthodox religion. About 44 (10.4%) and 128 (30.3%) of participants were smoking cigarette and drinking alcohol, respectively. Though (292, 69%) of the study participants' reported that they were doing physical exercise by walking, almost all of the participants (413, 97.6%) reported that they did not work a regular scheduled physical exercise. Out of the study participants, (245, 57.9%) of them were taking ≥three drugs prior to admission and (127, 30%) of the participants were taking ≥ five drugs which is termed as polypharmacy. Above half of the participants (213, 50.4%) had co-morbid diseases which have been hypertension (108, 25.5%), cardiac diseases (59, 13.9%) and diabetes mellitus (53, 12.5%) were predominant. The total length of hospital stays were 4352days with a mean (SD) of 10.28±8.99 days and ranges from 2 to 96 days.

Table 1: *Socio-demographic and clinical characteristics of the participants in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia, August to September, 2020 (n= 423)*

	Causes of Patients hospitalization		
Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Gender			
Male	119(48.6)	88(49.4)	207(48.9)
Female	126(51.4)	90(50.6)	216(51.1)
Age(in years)			
Mean± SD	48.23±17.85		
14 - 24	24(9.8)	14(7.9)	38(8.98)
25- 39	51(20.8)	59(33.1)	110(26)
40 - 64	100(40.8)	74(41.6)	174(41.1)
>64	70(28.6)	31(17.4)	101(23.9)
Marital status			
Single	64(26.1)	34(19.1)	98(23.2)
Married	129(48.6)	105(59)	234(55.3)
widowed	20(8.2)	9(5.1)	29(6.7)
Divorced	42(17.1)	31(16.9)	73(17.3)
Education level			
No formal education	116(47.3)	72(40.4)	188(44.4)
Elementary	66(26.9)	47(26.4)	113(26.7)
Secondary	31(12.7)	35(19.7)	66(15.6)
Tertiary	32(13.1)	24(13.5)	56(13.2)
Residence			
Addis Ababa	177(72.2)	127(71.3)	304(71.9)
Out of Addis Ababa	68(27.8)	51(28.7)	119(28.1)
Religion			
Orthodox	186(76)	136(76)	322(76.1)
Muslim	42(17.1)	31(17.4)	73(17.3)
Catholic	1(0.4)	1(0.6)	2(0.5)
Protestant	16(6.5)	10(6)	26(6.1)
Employment			
Employed	25(10.2)	25(14)	50(11.8)
Unemployed	0.0	1(0.6)	1(0.24)
House wife	30(12.2)	33(18.5)	63(14.9)
Merchant	13(5.3)	14(7.9)	27(6.4)
Student	18(7.3)	7(3.9)	25(5.9)

Table 1: *Socio-demographic and clinical characteristics of the participants in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia, August to September, 2020 (n= 423) Continued(1)……*

	Causes of Patients hospitalization		
Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Employment			
Laborer	51(20.8)	32(18)	83(19.6)
Retired	57(23.3)	40(22.5)	97(22.9)
Others[a]	29(11.8)	14(7.9)	43(10.2)
Farmer	22(9)	12(6.7)	34(8)
Social habit(smoking cigarette)			
Yes	29(11.8)	15(8.4)	44(10.4)
No	216(88.2)	163(91.6)	379(89.6)
Social habit(dining alcohol)			
Yes	71(29)	57(32)	128(30.3)
No	174(71)	121(68)	295(69.7)
Physical activity(walk)			
Yes	165(39)	127(71.3)	292(69)
No	80(32.7)	51(28.7)	131(31)
Physical activity (regular physical exercise)			
Yes	5(2)	5(2.8)	10(2.4)
No	240(98)	173(97.2)	413(97.6)
Other Drugs (including OTC, herbals)			
Yes	3(1.2)	0(0)	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Number of medications taken per patient			
Mean± SD	3.39±2.35		
0	24(9.8)	12(6.7)	36(8.5)
1	41(16.7)	26(14.6)	67(15.8)
2	35(14.3)	40(22.5)	75(17.7)
3-5	98(40)	75(42.1)	173(40.9)
>5	47(19.2)	25(14)	72(17)
Polypharmacy			
Yes	84(34.3)	43(24.2)	127(30)
No	161(65.7)	135(75.8)	296(70)
Co morbid diseases			
Yes	137(55.9)	76(42.7)	213(50.4)
No	108(44.1)	102(57.3)	210(49.6)

[a] Others: participants who did not have any occupation rather they were dependly living with another people. DRH, drug related hospitalization; Non-DRH, Non-drug related hospitalization; n,number;SD, standard deviation

Table 1: *Socio-demographic and clinical characteristics of the participants in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia, August to September, 2020(n= 423) Continued(2)……*

	Causes of Patients hospitalization		
Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Co morbid diseases (Hypertension)			
Yes	68(27.8)	40(22.5)	108(25.5)
No	177(72.2)	138(77.5)	315(74.5)
Co morbid diseases (Diabetes mellitus)			
Yes	31(12.7)	22(12.4)	53(12.5)
No	214(87.3)	156(87.6)	370(87.5)
Co morbid diseases (Asthma)			
Yes	7(2.9)	7(3.9)	14(3.3)
No	238(97.1)	171(96.1)	409(96.7)
Co morbid diseases (Hyperthyroidism)			
Yes	5(2)	1(0.6)	6(1.4)
No	240(98)	177(99.4)	417(98.6)
Co morbid diseases (Cardiac diseases[b])			
Yes	38(15.5)	21(11.8)	59(13.9)
No	207(84.5)	157(88.2)	364(86)
Co morbid diseases (Stroke)			
Yes	7(2.9)	7(3.9)	14(3.3)
No	238(97.1)	171(96.1)	409
Co morbid diseases (Dyslipidemia)			
Yes	4(1.6)	2(1.1)	6(1.4)
No	241(98.4)	176(98.9)	417(98.6)
Co morbid diseases (Schizophrenia)			
Yes	3(1.2)	0	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Co morbid diseases (CKD)			
Yes	5(2)	7(3.9)	12(2.8)
No	240(98)	171(96.1)	411(97.2)
Length of Hospital stay (Days)			
1─7	101(41.2)	112(62.9)	213(50.4)
>7	144(58.8)	66(37.1)	210(49.6)
Mean± SD	11.4±9.27		
Median	9		
Range	2-96		

[b]Cardiac diseases include heart failure, Chronic rheumatoid valvular heart disease, atrial fibrillation and Coronary artery disease.CKD=Chronic kidney disease; OTC=Over the counter

4.2. Prevalence and categories of drug related hospitalizations

Of the 423 enrolled patients, drug related hospitalizations were identified in 245 (57.9%) participants, of which 87.8% were deemed preventable. A total of 322 DRPs rendering DRHs were observed in 245 participants, representing 1.31 DRPs per patient, since 55(22.4%) patients presented two DRPs (***Figure 2***). Out of 245 drug related hospitalized patients, more than half (130, 53%) of them were noted from failure to receive drugs followed by untreated indication (94, 37.8%) and then sub-therapeutic dosage (30, 12.2%).The main reasons for failure to receive drugs were due to patients preferred not to take the medication (43, 33.1%); feared adverse events (18, 13.8%); and drug products were not available (17, 13.1%)

Table ***2***).

Table 2*:Categories of drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia, August to September, 2020 (n= 245)*

Categories of drug related hospitalizations	**Causes of drug related hospitalizations**	**Frequency (%)**
Untreated indications		94(38.5)
	Untreated medical condition is existed	34(36.2)
	Synergistic/ potentiating drug needed	42(44.7)
	Preventive/ prophylactic drug needed	18(19%)
Ineffective drug product/ Improper Drug Selection		16(6.5)
	More effective alternative drug is available	6(37.5)
	Condition is already refractory to drug	2(12.5)
	The drug is not effective for condition	6(37.5)
	Expired drugs(Salbutamol and insulin)	2(12.5)
Sub therapeutic Dosage		30(12.2)
	Wrong dose (too small) of the drug	24(80)
	Frequency is inappropriate (long)	5(16.7)
	Duration of drug use is too short	1(3.3)

Table ***2:Categories of drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia, August to September, 2020 (n= 245) Continued…***

Categories of drug related hospitalizations	**Causes of DRHs**	**Frequency (%)**
Supra therapeutic Dosage		13(5.3)
	Wrong dose (too high) of the drug	11(84.6)
	Frequency is inappropriate (short)	2(15.4)
Adverse drug reaction		38(15.5)
	Undesired effect from the drug is found	34(89.5)
	Unsafe drug for patient is existed	1(2.6)
	Dosage is administered or changed too rapidly	1(2.6)
	Allergic reactions is found/reported	2(5.3)
Drug Interactions		1(0.4)
	There is (are) major drug interaction	1(100)
Failure to receive drugs.		130(53.5)
	Does not understand instructions	6(4.6)
	Patients prefer not to take	43(33.1)
	Patients forget to take	3(2.3)
	Drug product not available	17(13.1)
	Cost of medication too expensive	16(12.3)
	Disbelieves on the drug effectiveness	1(0.8)
	Patients felt better	17(13.1)
	Patients felt worse	1(0.8)
	Fear of adverse events	18(13.8)
	Failure to follow-up due to Covid-19	8(6.2)
Total number of DRPs leading DRHs		322
Total number of participants with DRHs		245
Average number DRPs per patients with DRHs		1.31
Preventability of DRHs		215(87.8)

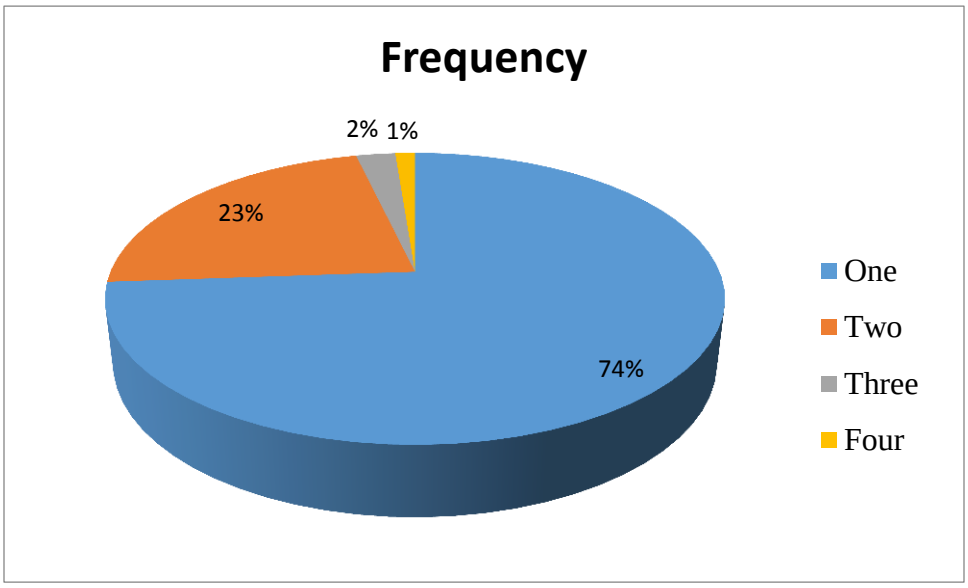

Figure 2: *Numbers of drug related problems occurrence per patient leading hospitalization in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia ,August to September, 2020 (n= 245)*

Table 3: *Examples of the various types of the identified drug related problems for the cause of drug related hospitalizations*

Examples of the various type of the identified DRPs for the cause of DRHs		
DRPs categories leading hospitalizations	**Examples**	**Preventability**
Failure to receive drugs	This was a 60 years old female known RVI[c] patient for the past 8 years and had been taking combination antiretroviral therapy for 4 years but discontinued for the past 1 year due to she feared adverse effect of the drugs. Eventually, she was admitted to ZMH with exacerbation of shortness of breath, seborrheic dermatitis, skin rash, watery diarrhea and weight loss.	Preventable
	This is a 43 years old known type I diabetes mellitus male patient. Though he was on human insulin (NPH) 20/14 IU, this drug was not taking for 5 days prior to the admission because of unavailability of the medication and then presented with poly symptoms like polyurea,polydypsia and polyphagia;vomiting of ingested matter and his random blood glucose level was 345 mg/dl. The diagnosis was type1 diabetes mellitus with severe diabetes ketoacidosis secondary to drug discontinuation.	
	A 14 years old known heart failure 2^{o} to CRVHD male patient for the last 05 years who presented with a chief compliant of worsening of shortness of breath, dry cough associated with history of orthopnea of 3 pillows and PND to TASH EW after he discontinued his medications (enalapril 5mg po/day, furosemide 20 mg po bid, spironolactone 25 mg PO/day and benzathine pencilline 1.2 million unit) because of the patient felt better.	
	A 67 years known hypertensive male patient for the past 2 years but not on treatment due to patients prefer not to take, admitted to TASH EW with a diagnosis of left side hemiplegia secondary to hemorrhagic stroke.	
Untreated indication and failure to receive drugs	A 56 years old male patient admitted to ZMH with left sided body weakness 8 days of duration and associated with unable to communicate since 6 days duration prior to his admission. He has old ischemic stroke medical history before 2years and a known diabetes mellitus patient on metformin 500mg po bid but discontinued 1 year ago because he preferred not to take any medication.	Preventable

[c] RVI=Retro Viral Infected; NPH=Neutral Protamine Hagedorn; 2^{O}=secondary; CRVHD=chronic rheumatoid valvular heart disease; PND=paroxysmal nocturnal dyspnea; PO=by mouth; BID=twice a day.

Table 3: *Examples of the various types of the identified drug related problems for the cause of drug related hospitalizations Continued…*

Examples of the various type of the identified DRPs for the cause of DRHs		
DRPs categories leading hospitalizations	**Example**	**Preventability**
Untreated indication ,improper drug selection and subtherapeutic dosage	A 44 years old male heart failure patient secondary to CRVHD admitted to Y12HMC with a chief complaint of bilateral leg swelling ,easy fatigue ability and shortness of breath since 1 month of prior to his admission. He was prescribed furosemide 80 mg po tid[d], warfarin 7.5 mg po/day, spironolactone 100 mg po/day, digoxin 0.125 mg po/day and Atenolol 50mg po tid before he was admitted but the patient was taking furosemide 80 mg po/day and all other drugs as they were prescribed. Here, ACEI is important but not indicated and also metoprolol is more preferable than Atenolol.	Preventable
Subtherapeutic dosage	A 80 years old known diabetes mellitus male patient ,for the past 10 years, was on follow up taking metformin 500 mg po bid but since 5 months back ,he was taking metformin 500 mg only on the evening and presented with a chief compliant of poly symptoms to Y12HMC and diagnosed with uncontrolled diabetes mellitus with dosage too low	Preventable
Improper drug selection	This was a 50 years old female patient was treated with anti tuberculosis medications for three months but did not get an improvement and admitted in TASH with chief compliant of worsening of shortness of breath, hemoptysis and chest pain and diagnosis was advanced lung cancer with malignant pleural effusion.	preventable

[d]tid=three times a day; DKA= Diabetic ketoacidosis

Table 3: *Examples of the various types of the identified drug related problems for the cause of drug related hospitalizations Continued….*

Examples of the various type of the identified DRPs for the cause of DRHs

DRPs categories leading hospitalizations	Example	Preventability
ADR	A 22 years old female patient who admitted to Y12HMC with generalized skin rash of 1 week after she was taking amoxicillin 500 mg po tid and cephalexin in different time for tonsilophyringitis but rash has been worsening and diagnosed with toxic epidermal necrosis secondary to amoxicillin and cephalexin reactions.	Non-preventable
	This was a 71 years old female known heart failure patient on aspirin 81 mg po/day, atorvastatin 20 mg po/day, metoprolol 12.5 mg po/day, furosemide 40 mg po/day, spironolactone 25mg po/day. She was visited to TASH EW after she took all of the medication at the same time and experienced retrosternal chest pain, regurgitation and abdominal pain. The pain was occurred after the ingestion of the drugs and the diagnosis was dyspepsia secondary to drugs. It was most likely linked with ingestion of aspirin along with others.	Preventable
Suprathrapeutic dosage	A 35 years old diabetes mellitus male patient admitted with loss of consciousness of 3 days duration due to hypoglycemia (RBS[e]=25mg/dl) induced brain injury secondary to insulin over dose(64/100).	Preventable
	A 27 years old female patient who was a known schizophernic patient for the past 3 years on amitriptyline 25 mg po/day which was changed to resperidone 4mg po/day before 2 days of her admission to ZMH. But, she took 15 pills (60mg)of resperidone at one dose and later on she experienced with generalized body weakness,hypotension (BP=85/45)and tachycardia(PR=135).	Preventable

[e] RBS=random blood sugar;BP=blood pressure;PR=pulse rate

4.3. Medications and diseases involved in drug related hospitalizations

Among the total 245 drug related hospitalized patients, nearly one third of them had

the cardiovasc1ular diseases (80, 32.6%), of which heart failure accounted for (59, 24%) followed by endocrine diseases(47,19.2%) with the prominent disease of diabetes mellitus(44,18%) and cerebrovascular disease which was stroke(26,10.6%).Patients who had HIV(15, 6.1%) and asthma (14, 5.7%) also accounted for more than 10% of DRHs as presented in *Table 4*.

A total of 497 numbers of drugs were pertained to 245 patients DRHs. This reflects that 2.03 drugs per patient were involved in DRHs. Of these, cardiovascular, chemotherapeutic and endocrine drug classes were the most frequently involved drugs which contributed to hospital admissions. Among cardiovascular drugs; furosemide(59,24.1%),angiotensin converting enzyme inhibitors(ACEIs)(48,19.1%), and antiplatelets and anticoagulants(44,18%) were most frequently mentioned followed by drugs act on the endocrine system; oral hypoglycemic agents (37, 15.1%) and insulin(24, 9.8%) .And also, the chemotherapeutic drugs such as antibiotics(25 ,10%), Anticancer drugs (23 ,9%),and combination antiretroviral therapy(15 , 6.1%)were associated to the patients DRHs. Medication classes and specific drugs reported in DRHs depicted in *Table 5*.

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Table 4: *Diseases that associated with drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia ,August to September, 2020 (n= 245)*

Diseases categories(n)	Name of specific disease	n,(%)
	[f]PAD	6(2.4)
	Hypertension	9(3.7)
Cardiovascular diseases (n=80, 32.6%)	**Heart failure**	**59(24)**
	DVT	5(2)
	Ischemic heart disease	1(0.4)
	Schizophrenia	2(0.8)
CNS diseases (n=**8, 3.2%)**	Epilepsy	6(2.4)
Cerebrovascular disease (n=**26, 10.6%)**	**Stroke**	**26(10.6)**
	Tuberculosis	6(2.4)
Infectious diseases (n=**21, 8.5%)**	**HIV**	**15(6.1)**
	Colonic Cancer	2(0.8)
	Hematological malignancy	2(0.8)
	Melanoma	1(0.4)
	AML	3(1.2)
	NHL	3(1.2)
	Gastric Cancer	1(0.4)
	Lung cancer	2(0.8)
	MDS	1(0.4)
	HL	1(0.4)
	CLL	1(0.4)
	Hair cell leukemia	1(0.4)
Diseases of cancer (n=**25, 10.1%)**	Breast cancer	3(1.2)
	Cervical cancer	2(0.8)

[f]PAD ,Peripheral arterial disease ;DVT ,Deep venous thromboembolism;HIV, Human immunodeficiency virus;AML ,acute myeloid leukemia ;NHL ,non-hodking lymphoma; MDS ,myelodysplastic syndrome; HL, hodkin lymphoma; CLL, chronic lymphoid leukemia

Table 4: *Diseases that associated with drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia ,August to September, 2020 (n= 245) Continued….*

Diseases categories (n)	Name of specific disease	n,(%)
	[g]ALL	1(0.4)
	Myelofibrosis	1(0.4)
	Thyroid storm	1(0.4)
Endocrine system diseases (n=47,	**Diabetes mellitus**	**44(18)**
19.2%)	Hypoglycemia	2(0.8)
	COPD	3(1.2)
Diseases of the respiratory system	Bronchoectiasis	3(1.2)
(n=**21,**	**Asthma**	**14(5.7)**
8.5%)	Corpulmonal	1(0.4)
	Dyspepsia	5(2)
GI diseases (n=**10, 4%)**	CLD	5(2)
	TEN	1(0.4)
	Anemia	2(0.8)
	CKD	2(0.8)
	SLE	1(0.4)
Others (n=**7, 2.8%)**	Hemophilia	1(0.4)
	TOTAL	245(100)

[g]ALL,acute lymphoid leukemia;COPD,chronic obstructive pulmonary disease;CLD,chronic liver disease;TEN,toxic epidermal necrosis;CKD,chronic kidney disease;SLE,systemic lupus erythomatous

Table 5: *Medication classes and specific drugs implicated in drug related hospitalizationsin emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia ,August to September, 2020 (n= 245)*

Drugs involved in DRHs		
Drugsclass	**Specific drugs**	**n(%)**
Cardiovascular drugs		
	Atorvastatin	31(12.7)
	Antiplatelets(aspirin,clopidogril)	24(9.8)
	Furosemide	59(24.1)
	Spironolactone	33(13.5)
	Anticoagulants(Warfarin, heparin)	20(8.2)
	Beta blockers (metoprolol,atenolol)	21(8.6)
	Digoxin	15(6.1)
	Angiotensin converting enzyme inhibitors (enalapril/lisnopril)	48(19.6)
	Calcium channel blockers (nifedipine,amlodipine)	34(13.9)
	Hydrochlorothiazide	11(4.5)
Drugs act on the respiratory system		
	Long acting beta agonist	15(6.1)
	bronchodilator	10(4.1)
Central nervous system drugs		
	Antiepileptics	5(2)
	antipsychotic	5(2)
	Amitriptylin	2(0.8)
Chemotherapeutic drugs		
	Antibiotics(piperacillin/tazobactam,meropenem,amoxicillin, amoxicillin/clavunic acid ,ceftriaxone,benzathinepenicillin)	25(10.2)
	Combination antiretroviral therapy	15(6.1)
	Anti-tuberculosis	13(5.3)
	Anticancer drugs	23(9.4)

Table 5: *Medication classes and specific drugs implicated in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia ,August to September, 2020 (n= 245) Continued….*

Drugs involved in DRHs		
Drugs class	**Specific drugs**	**n (%)**
Immuno-suppressants		
	Mycophenolate	1(.4)
	corticosteroids (prednisolone,budesonide)	9(3.7)
Endocrine drugs		
	Oral hypoglycemic drugs(metformin,glibenclamide)	37(15.1)
	Insulin	24(9.8)
	Propylthiouracil	4(1.6)
Gastrointestinal drug	Proton pump inhibitors	7(2.9)
Others		
	Potassium chloride	1(0.4)
	Non-steroidal anti-inflammatory drugs	3(1.2)
	Opioid	1(0.4)
	Ferrous sulphate	1(0.4)
Total number of medications involved in DRHs		497
Total number of participants with DRHs		245(57.9)
Average number medications per patients with DRHs		2.03

4.4. Factors associated with the occurrence of drug related hospitalizations

Univariate analysis showed that age, educational level, marital status, employment, number of medications taken, presence of co morbid diseases and length of hospital stay have been revealed p-value which was less than 0.2 (*Table 6*) and they were incorporated for multivariate binary logistic regressions. According to the multivariate analysis, five variables were significantly associated with the occurrence of DRHs. Those statistically significant correlations with the occurrence of DRHs were found in age, employment, presence of co morbid diseases, length of hospital stay and education level. From the Adjusted Odds Ratio (AOR) for age (AOR=7.451,

95%CI: 1.889-29.397, P=0.004) which indicated that an increased age would make to develop DRHs. Tertiary educational level (AOR=0.360, 95%CI: 0.141-0.923, P=0.033) which indicates that being literate protect the participants from DRHs by 64% as compared to participants who had no formal education.

Among the employment ,participants who did not have any occupation which were specified as others in *Table 1*(AOR=3.409 ,95%CI:1.120-10.374,P=0.031)were 3.4 times more likely to be hospitalized due to drug related morbidity than non-drug related while compared to the employed one and students were more than 6 times high likely to had DRHs than non-drug related hospitalizations while compared to the employed participants (AOR=6.33 ,95%CI:1.375-29.153,P=0.018).

Participants with two or more diseases (co-morbid diseases) were 2 times high likely to contract DRHs than non-drug as compared to participants without co morbid diseases (AOR=2.004,95%CI: 1.095-3.668,P=0.024),and regarding patients hospital stay, participants with DRHs were 2.2 times more likely stayed> 7 days than patients with non drug related hospitalizations as estimated to < 7 days of length of hospital stayment after their admission (AOR=2.186,95%CI: 1.412-3.382,P=0).

Table 6:*Predictors that involved in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia ,August to September, 2020 (n= 245)*

	Causes of Patients hospitalization			**Odds Ratios**		
	[h]DRH(245)	**Non-DRH(178)**	**Total(423)**	**COR(95% CI)**	**AOR(95% CI)**	**P-value**
Covariates	**n (%)**	**n (%)**	**n (%)**			
Age (Years)						
Mean±SD	48.24±17.86		47.50± 17.21			
14 - 24	24(9.8)	14(7.9)	38(8.98)	1.000	1.000	0.006
25- 39	51(20.8)	59(33.1)	110(26)	0.759(0.347-1.661)	1.551(0.515-4.668)	0.435
40 - 64	100(40.8)	74(41.6)	174(41.1)	0.383(0.218-0.674)	2.567(0.818-8.056)	0.106
>64	70(28.6)	31(17.4)	101(23.9)	0.598(0.356-1.00)	7.451(1.889-29.397)	**0.004**
Marital status						
Single	64(26.1)	34(19.1)	98(23.2)	1.000	1.000	0.296
Married	129(48.6)	105(59)	234(55.3)	0.602(0.368-0.985)	0.598(0.292-1.225)	0.160
Widowed	20(8.2)	9(5.1)	29(6.7)	0.744(0.397-1.392)	0.486(0.201-1.176)	0.109
Divorced	42(17.1)	31(16.9)	73(17.3)	1.181(0.485-2.874)	0.345(0.158-0.752)	0.983
Education level						
No formal education	116(47.3)	72(40.4)	188(44.4)	1.000	1.000	0.183

[h]DRH,drug related hospitalization;Non-DRH, non drug related hospitalization; COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval

Table 6:*Predictors that involved in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC,Addis Ababa, Ethiopia ,August to September, 2020 (n= 245) Continued….*

Elementary	66(26.9)	47(26.4)	113(26.7)	0.872(0.542-1.403)	0.569(0.227-1.427)	0.229
Secondary	31(12.7)	35(19.7)	66(15.6)	0.550(0.312-0.968)	0.566(0.230-1.391)	0.215
Tertiary	32(13.1)	24(13.5)	56(13.2)	0.828(0.452-1.516)	0.360(0.141-0.923)	**0.033**
Employment						
Employed	25(10.2)	25(14)	50(11.8)	1.000	1.000	0.156
Unemployed	0	1(0.6)	1(0.24)	0.483(0.207-1.124)	0.293(0.096-0.893)	1.000
house wife	30(12.2)	33(18.5)	63(14.9)		1.798(0.649-4.978)	0.259
merchant	13(5.3)	14(7.9)	27(6.4)	0.439(0.196-0.984)	1.809(0.555-5.892)	0.325
Student	18(7.3)	7(3.9)	25(5.9)	0.448(0.167-1.204)	6.331(1.375-29.153)	**0.018**
Day laborer	51(20.8)	32(18)	83(19.6)	0.885(0.342-2.287)	2.643(0.995-7.023)	0.051
Retired	57(23.3)	40(22.5)	97(22.9)	0.769(0.354-1.672)	0.982(0.345-2.795)	0.973
Others	29(11.8)	14(7.9)	43(10.2)	0.688(0.323-1.464)	3.409(1.120-10.374)	**0.031**
farmer	22(9)	12(6.7)	34(8)	1.241(0.421-3.660)	2.887(0.890-9.364)	0.077
Polypharmacy						
Yes	84(34.3)	43(24.2)	127(30)	1.638(1.062-2.525)	1.481(0.722-3.037)	0.284
No	161(65.7)	135(75.8)	296(70)	1.000	1.000	
Co morbid diseases						
Yes	137(55.9)	76(42.7)	213(50.4)	1.702(1.153-2.514)	2.004(1.095-3.668)	**0.024**
No	108(44.1)	102(57.3)	210(49.6)	1.000	1.000	
Hospital stay (days)						
1─7	101(41.2)	112(62.9)	213(50.4)	1.000	1.000	
>7	144(58.8)	66(37.1)	210(49.6)	2.419(1.627-3.597)	2.186(1.412-3.382)	**0.000**

5. Discussion

The aim of optimizing pharmacotherapy is to achieve the desired therapeutic outcomes in the absence of morbidity and mortality associated with the drug. To the best of our knowledge, this study is the first to explore the prevalence, categories and rate of preventability of DRHs in ED at three selected hospitals, Addis Ababa, Ethiopia.

The occurrence of DRHs was high (245,57.9%) and is substantially utmost from other studies conducted in America (16.2%), Brasil (31.6%) , Denmark (10.8%) ,Norway(38%),Sewdin (41.3%),Greece(12.8%) %,India(17.2 %), and Malaysia (39%)(Kent M. Nelson, 1996, Alexopoulou et al., 2008, Andreazza et al., 2011, Dammalapati et al., 2018, J. HALLAS, 1990, Karuppannan et al., 2013, Lea et al., 2019, Gustafsson et al., 2016).The high prevalence in the current study could be explained by numbers of reasons:(1) The categories of DRPs causing DRHs investigated in the present study were comprehensive, whilst other studies only investigated particular types of DRPs resulted DRHs such as therapeutic failure(Karuppannan et al., 2013) and ADR (Alayed et al., 2019, Alexopoulou et al., 2008, Geer et al., 2016, Parameswaran Nair et al., 2016);(2) the prospective design of this study helps to ensure that all information required to accurately classify the events were gathered;(3)detailed histories of drug therapy obtained by clinical pharmacists may improve detection of DRHs ;and(4) use of the Helper's and Strand's comprehensive classification system has likely boosted the probability that all possible drug-related causes of hospitalization to be identified. Largely, the wide variability in the incidence of DRHs may be attributed to the variations in the extent of study population, inclusion criteria, study settings, participant's level of education and awareness, level of health professional expertise, scope of evaluating DRHs attributed to DRPs ,study designs (prospective vs. retrospective) and the study duration. These variations of reasons also reported by other studies (Alayed et al., 2019, Geer et al., 2016, Parameswaran Nair et al., 2016, R L Howard, 2003, Singh et al., 2011).

In this study, 87.8 % of DRHs were deemed to be preventable which is agreed with other international studies in which preventability of DRHs has been by far greater than fifty percent (Dammalapati et al., 2018, Leslie Jo Samoy, 2006, Mohamed Al-Arifi and Aljadhey, 2013,

Parameswaran Nair et al., 2016, Peter J. Zed, 2015, R L Howard, 2003, Singh et al., 2011, Yosef H. Al-Olah, 2008).In the present study, the reasons why DRHs preventability has been high due to they have not been appeared if possible measurements could be taken prior to drug related diseases. For instance, the principal categories of DRHs in our study were failure to receive drugs(130,53.5%) and untreated indication(94, 38.5%).Hence, both DRHs attributed to DRPs could be avoided by providing awareness for patients about their drugs use, applying good prescribing and dispensing practice, and making appropriate pharmaceutical care plan.

The majority of DRHs were seen among female patients which is concordant with what has been done in the previous study (Nivya et al., 2015). However, in study done in Saudi Arabia, DRHs were largely found in male patients(Mohamed Al-Arifi and Aljadhey, 2013, Alayed et al., 2019).Elderly patients encountered more DRPs leading to DRHs than patients in other age groups which also in line with other studies (Gustafsson et al., 2016, Karuppannan et al., 2013, Linkens et al., 2020).The main reasons could be as patient's age is becoming advanced; physiologic functions are being deteriorated and presence of likelihood of co morbid conditions which may predispose them to taking of multiple drugs concomitantly which ultimately basis for the patients to contract medication side effects, interactions(drug-drug or drug-food) thereby failure to receive drugs will occur owing to patients non adherence to their regimens, fear of drugs side effect, unavailability of the drugs and expensiveness of the medications.

Patients whose education level being elementary and below were more prone in developing DRHs than having education high school or above which was consistent with studies done previously (Andreazza et al., 2011, Dammalapati et al., 2018).This could be related to high level education might be useful to understand about appropriate medications use. More than half of DRHs also accounted from patients whose occupations were day laborer, retired and patients lived in dependency stated as others in *Table 1*.It could be associated with that of they could not afford their drugs and cultural issue.

Of the 245 patients with DRHs, the foremost category of DRHs in this study was failure to receive drugs (130,53.5%) followed by untreated indication (94,38.5%),adverse drug reaction(38,15.5%) and sub therapeutic dosage (30,12.2%).The findings were reported with other studies (Ayalew et al., 2019, Dammalapati et al., 2018, Karuppannan et al., 2013, Kent M.

Nelson, 1996, Leslie Jo Samoy, 2006, Marcum et al., 2012, Mohamed Al-Arifi and Aljadhey, 2013, Peter J. Zed, 2015, Yosef H. Al-Olah, 2008).The major reasons for failure to receive drugs in present study were patients preferred not to take the drugs rather they preferred others cultural and religious activities, drug products were not available, cost of medications was too expensive, fear of adverse events, failure to follow-up due to Covid-19, and they felt better and near to half of patients with DRHs were participants have no formal education. Therefore, inability to recall the regimen were other important reasons associated with increased risk of a hospitalization related to failure to receive drugs which was mentioned in the past study (Andreazza et al., 2011, Leslie Jo Samoy, 2006, Singh et al., 2011).

The second frequent category of DRHs was untreated indication (94, 38.5%) as it was reported in others ((Mohamed Al-Arifi and Aljadhey, 2013, Pellegrin et al., 2017).Reasons were patients remained untreated; prophylaxis and synergistic medications were not indicated. This might be due to incorrect diagnosis, patients didn't come to health setting timely and treating physicians did not follow the management guidelines/protocols. For example, patients having moderate persistent asthma were being treated with albuterol inhalation alone and statins have not been indicated for patients with atherosclerotic cardiovascular disease (ASCVDs) like peripheral arterial disease, stroke, ischemic heart disease and whose age $\geq$ 40 years with diabetes mellitus and high low density lipoprotein level. In addition, some compelling indication like hypertension remains untreated and subsequently results in DRHs owing to stroke and others cardiovascular diseases. Furthermore, since only cancer diagnosis and management are carried out in one of this research setting hospital which is TASH, patients come from different Ethiopia places were remained untreated and predisposed to various empirical therapies like anti-tuberculosis drugs for lung cancer that also lead to improper drug selection until they treat with anti-cancer drugs in TASH.

Adverse drug reactions (38, 15.5%) were also commonly reported as the common classifications of DRHs which is also mentioned with other studies (Hohl et al., 2011, J. HALLAS, 1990, Kent M. Nelson, 1996, Leslie Jo Samoy, 2006, Parameswaran Nair et al., 2016, Peter J. Zed, 2015, Singh et al., 2011). This might be associated with numerous numbers of cardiac and diabetic patients in our study population and poor awareness of patients with regard to cardiac medications untoward effects such as diuretics inducing electrolytes disturbance and

hypoglycemic symptoms of Antidiabetics, respectively might be plausible explanations for increased ADRs. Some ADRs could be resulted from disobeying of direction for use of the medications. For example, diabetes mellitus patient who was on metformin experienced epigastric burning sensation pain and vomiting after metformin was being taken without meal. Overall, the plausible explanations for DRHs might be the absence of pharmaceutical care services in many health institutions including those wards of the study settings that is very important to optimize drug therapy and patient safety and also there were a poor collaboration among patients, clinical pharmacists and physicians about patient's medications use process involving medications use, their side effects, adherence issue and consequences if they will not take their medication properly. Therefore, the better opportunity for pharmacists to add value in patient care roles is through ensuring medication management services according to evidence-based guidelines. Both failure to receive drugs and untreated indication for which need additional drug therapy were mentioned in the present study as a main categories of DRPs resulted DRHs were supported by other study (Pellegrin et al., 2017, Dammalapati et al., 2018, Lea et al., 2019).

In this study finding, medication classes that were frequently reported as causing of DRHs were cardiovascular medicines, chemotherapeutic drugs, endocrine drugs, respiratory medicines and central nervous system drugs. Among these classes of drugs, cardiovascular drugs were predominantly involved in DRHs which was in line with other studies (Andreazza et al., 2011, Ayalew et al., 2019, Gustafsson et al., 2016, Karuppannan et al., 2013, Leslie Jo Samoy, 2006, Marcum et al., 2012).Cardiovascular drugs, antidiabetics, and antiasthmatics were most commonly associated with DRHs was supported in the previous studies (Alayed et al., 2019, Alexopoulou et al., 2008, Daniel S. Budnitz, 2011, Karuppannan et al., 2013).The most common drugs associated with DRHs mentioned in this finding were furousemide, ACEIs ,insulins, oral hypoglycemic agents, warfarin, spironolactone, aspirin and central nervous system agent and those were implicated in the previous studies (Ayalew et al., 2019, Daniel S. Budnitz, 2011, Lea et al., 2019, Leslie Jo Samoy, 2006, Mohamed Al-Arifi and Aljadhey, 2013, Parameswaran Nair et al., 2016, R L Howard, 2003).The main reasons in this study might be connected with the common diseases of the study area which were heart failure, diabetes mellitus, stroke, human immunodeficiency virus and asthma. For those diseases, the above mentioned drugs have been participated.

Moreover, the most common organ system involved in DRHs was the cardiovascular system (80, 32.6%), with the most common specific disease of heart failure (59, 24%) which is consistent with the previous studies (Gustafsson et al., 2016, Marcum et al., 2012). Moreover, hypertension was mentioned for DRHs which was implicated in the previous study (Ayalew et al., 2019, Karuppannan et al., 2013, Mohamed Al-Arifi and Aljadhey, 2013)**.**This is due to cardiovascular diseases require multiple medicine regimens and this contributed to DRPs. All hospitalizations attributed to endocrine agents were for hypoglycemia, hyperglycemia and diabetic ketoacidosis which was also cited in the other study(Karuppannan et al., 2013, Mohamed Al-Arifi and Aljadhey, 2013).It might be due to the patients poor awareness about the hypoglycemic symptoms of anti hypoglycemic agents , poor monitoring control and patients prefer not to take the medications.

In this finding; predictors independently influence DRHs such as age, educational level and presence of co morbid disease had statistically significant correlation with the occurrence of DRHs. The findings are consistent with other studies (Dammalapati et al., 2018, Nivya et al., 2015, Peter J. Zed, 2015).Length of hospital stay also described in another studies (Dammalapati et al., 2018, Kent M. Nelson, 1996).

From factors which illustrated significant association in multiple binary logistic regression, patients with 65 years of age or older were 7.45 times more likely to be hospitalized due to drug related morbidity than non drug related as compared to age between 14 and 24 years. This might be owing to age-related physiological changes, larger number of coexisting disease conditions which require multiple medications have been associated with an increased risk of DRHs.

From employment factor, students were 6.3 folds high likely exposed to DRHs than non drug related as compared to the employed. This might be explained by the nature of the disease they had which means students in this finding have majorly contracted heart failure disease secondary to chronic rheumatoid valvular heart disease. Consequently, it needs lifelong and multiple medications treatment and then they faced various DRPs leading hospitalizations. Moreover, participants who did not have any occupation rather they lived with others in depending situation were 3.4 times high likely to be hospitalized owing to drug related diseases than non drug related as compared to employed.

The other factor was education level in which patients with tertiary education level were 64% less likely to be hospitalized with drug related hospitalizations as compared to participants who did not have formal education. This could be related to high level education might be useful to understand about appropriate medications use. This was supported by the studies (Andreazza et al., 2011, Dammalapati et al., 2018, Singh et al., 2011). Patients with co morbid disease were also 2 folds high likely to be drug related hospitalized than non-drug related as compared to patients without co morbid disease. As implicated in the previous studies (Dammalapati et al., 2018, Nivya et al., 2015, Peter J. Zed, 2015), co- morbidity increases the vulnerability towards DRPs. These results clearly indicate the necessity of managing DRHs in multimorbid patients.

Patients with DRHs were 2.2 times more likely stayed for > 7 days after they were hospitalized than patients with non-drug related hospitalization with estimated to less than 7 days of length of hospital stay. The overall length of the hospital stay in the present study was 2788 days with the average length of hospital stay 11.4±9.27 days, which is longer than what has been reported in other studies (Yosef H. Al-Olah, 2008).This was might be owing to the data in the previous study is in a single hospital and for a relatively short period of time (28 days)while in this finding, the study was carried out at three hospitals for the periods of 60 days.

Among factors which have not demonstrated an association in multivariate analysis, polypharmacy was mentioned. This agree with what have been reported in other studies(Leslie Jo Samoy, 2006, Marcum et al., 2012).In contrast, polypharmacy has been reported having positive association with the occurrence of DRHs in the previous literatures (Andreazza et al., 2011, Gustafsson et al., 2016, Mohamed Al-Arifi and Aljadhey, 2013, Singh et al., 2011).This insignificance could be resulted from variations in numbers of used medications and identified DRPs for causing DRHs. In this study, around two third of the patients with DRHs were using from none to four drugs per patient. Accordingly to say polypharmacy; ≥ five drugs should be concomitantly taken. Furthermore, the identified DRPs causing DRHs were failure to receive drugs and untreated indication. So, both categories reveal not taking medications and the patients might not used polypharmacy. Additionally; marital status did not illustrate significant association with DRHs.

6. Limitations of the study

The strength of this study was presented in terms of the study design which was prospective observational study in which different categories of DRPs leading hospitalizations can be easily identified through direct involvement of the patients and thereby it helped the sample size to be high. And also, the study was carried out in three hospitals of Addis Ababa, Ethiopia. Therefore; representativeness of the finding is more accepted and convinced. One of the main limitations of this study was there are no standardized protocols for immediately recording and reporting DRHs which may limit the estimation of real drug related hospitalized cases and leads to misdiagnosis of actual DRHs. This vagueness was mitigated by using clinical pharmacists who have an ability to identify and resolve DRPs. As this study conducted in EW,considerable numbers of patients with DRPs from other major departments have been missed and cross sectional study design by its nature does not determine the causality between the dependent and independent variables. Absence of country based specific diseases guidelines might affect our decision and impart some incomparability of our data with other assessments. Finally, the high number of patients with multiple disease conditions (co morbidities) might have confounded the assessment for DRHs. Future researches should better recognize such limitations.

7. Conclusion and recommendations

7.1 Conclusion

The prevalence of DRHs was significant (245, 57.9%).DRHs prevalence was common among emergency ward patients in the study settings. More than four fifth of DRHs were judged to be preventable. Among the total patients having DRHs, failure to receive drugs and untreated indication were the most frequently reported causes of DRHs. Amid factors; Age >64 years, tertiary education level, participants who did not have any occupation, students, presence of co-morbid diseases and length of hospital stay > 7 days have had significant association with DRHs.

7.2. Recommendations

In this finding, the prevalence of DRHs was common. Hence, researches regarding DRHs should be conducted in different Ethiopian hospitals to demonstrate its impact. Appropriate DRPs for the cause of DRHs formats should be aptly designed and incorporated in the patients' medical chart to record them and improve pharmaceutical care services. Clinical pharmacy services should be delivered in different wards of the hospitals. In addition, clinical pharmacists in three hospitals should provide awareness for physicians and residents regarding various DRPs causing DRHs in the morning session and health professionals team round. Minster of health should provide due attention for clinical pharmacy services and establish a system to account the clinical pharmacists. To evaluate the causality of DRPs leading hospitalizations, cohort study might be needed. Corrective, preventive and educational strategies should be provided on the most frequently involved drug-related hospitalized patients group. In addition, enforced counseling and education are needed for patients receiving diuretics like furousemide and spironolactone, ACEIs, insulin, antiasthmatics, chemotherapy, oral hypoglycemic agents and anticoagulants. Therefore, patients, caregivers/families, nurses, physicians and pharmacists should be collaborate more closely to provide and reinforce pharmaceutical care and monitor patients to prevent drug related visits to the emergency department and subsequent morbidity and mortality.

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ANNEXES

Annex 1: Information sheet and informed consent

Study's Information sheet

Addis Ababa University, College of Health Sciences, School of Pharmacy

Study Title: Prevalence and predictors of drug related hospitalization at multicenter study, Addis Ababa, Ethiopia.

Name of the principal investigator: Mulate Belete Demessie

Study areas: At Tikur Anbessa Specialized Hospital, Zewditu Memorial Hospital and Yekatit 12 Hospital Medical college.

Research budget: Will be covered by Addis Ababa University

Research objective: To assess prevalence and predictors of drug related hospitalization at multicenter study, Addis Ababa, Ethiopia.

Risks participants' experience: No potentially known risks contracted to patients

Benefit of study outcomes: After completion, the outcome of this study is expected to minimize drug related hospitalization by optimization of drugs utilization and which results in reducing morbidity and mortality of patients, for future planning, and for making health policies related to drug related hospitalization

Incentives to participants due to their participation: no other than acknowledgment**.**

Confidentiality: The study result will not include patient's name and any specific data of the patient will not be disclosed

Contact address to access the principal investigator (PI): If there is any inconvenience or doubt about the study, please contact:

MULATE BELETE DEMESSIE:

Phone No: +251-9-21-04-29-32

E-mail: beletemuler@gmail.com

Informed consent

Name of the investigator: MulateBeleteDemessie

Research title: Prevalence and predictors of drug related hospitalization at multicenter study, Addis Ababa, Ethiopia

Card number:_____ Code number_____

1. I, confirm that, I understand the information sheet for this study and have had the opportunity to ask questions.

2. I, understand that my participation is completely voluntary, and that I am free to withdraw at any time, without giving any reason, without legal rights being affected.

3. I understand that my response will be looked, and secured and necessary information will be extracted. I give you a permission to have an access to all my response.

4. I, agree to take part in the above study. I would like to confirm my agreement by signing.

Participant's name _____ Signature:_____date_____

Data collector's name:_____Signature:_____date_____

I thank you very much for your willingness to participate honestly and cooperatively!

Annex 2: Patients demographic and clinical data

IC card……..DOA……..Date of discharge…….

Part I: Socio-Demographic Characteristics						
1.Age (in years)		2.Sex	Male ☐	Female ☐		
3.Marital status		Single ☐	Married ☐	Divorced ☐	Widowed ☐	
4.Religion		Orthodox	Muslim	Catholic ☐	protestant ☐	others ☐
5.Educational status		No formal ☐	Grade 9-10 ☐	College diploma ☐		
		Grade 1-8 ☐	Grade 10-12 ☐	University degree and above ☐		
6. Residence (current)		Addis Ababa ☐	Out of Adds Ababa ☐			
7. Employment type		Employed ☐	Unemployed ☐	house wife☐merchant☐Student☐daily laborer ☐farmer		
		Others----------				
8. Social habits	Cigarette Smoker	Yes ☐	No ☐	Alcohol Drinker	Yes	No
9.Physical activity	Walk	Yes	No	Sport	Yes	No

Part II: Clinical characteristics	
1.Chief complaint	
2.Name of the disease	
3.Other Drugs (including OTC, herbals)	No ☐ Yes ☐ If yes list them and their purpose of use (indications)
4.Comorbid condition	No ☐ Yes ☐ If yes list here
5. Length of hospital stay(LOS)……	6.Average patient service cost/day……..

Part III: Data abstraction formats on taken patient histories, laboratory investigations, physical examinations and diagnostic imaging techniques

Weight (kg) _____ Height (cm) _____ Body mass index (BMI) [kg/m^2] _____

1. **Past medical conditions and medications**

Indication	Drug product (Generic Name)	Full Dosage regimen	Date (dd/mm/yy)		Response Effectiveness/ safety profile
			Started	Stopped	

2. Past medical history (hospitalizations, surgical procedures, injuries, pregnancies and so on)

PMH: _____

PSH: _____

Injuries: _____

3. Physical Examination (PE)/**vital** signs: Consecutive record of visits

	First visit				**Second Visit**				**Third visit**			
Date(dd/mm/yy	BP	PR	RR	T^0	BP	PR	RR	T^0	BP	PR	RR	T^0
SaO_2												

Any Pertinent physical examination and/or Review of systems findings:

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4. Pertinent **laboratory and imaging** series results (Findings for three consecutive results).

Lab Investigations		Date(dd/mm/yy)	Date(dd/mm/yy)	Date(dd/mm/yy)
Parameters				
Blood glucose level	HbA1c (%):			
	FBS(mg/dL):			
	RBS(mg/dL):			
Lipid panels	TC: mg/dl			
	LDL: mg/dl			
	TG: mg/dl			
	HDL: mg/dl			
RFTs	BUN/Scr			
	eGFR			
LFTs	AST			
	ALT			
	ALP			
	Bil/Alb			
Coagulation profile	PT			
	INR			
	PTT			
Serum electrolyte	Na^{+}/Cl^{-}			
	$Mg^{2+/}K^{+}$			
	$Ca^{2+/}Po_4^{3-}$			
CBC	WBC/N/L			
	RBC/Hgb/Hct			
	MCV/MCH			
	Plt			
Others				

Any diagnostic tools/Imaging techniques/modalities with findings			
Technique	Date(dd/mm/yy)	Date(dd/mm/yy)	Date(dd/mm/yy)

Annex 3: Categories of drug related problems leading hospitalizations

Categories	Common cause of drug therapy problem
drug use without indication	No medical indication of the drug is found Duplication of drug therapy is existed Non drug therapy should be indicated Drug is used in treating avoidable ADR Others ,specify_____
Untreated indication	Untreated medical condition is existed Preventive/ prophylactic drug needed Synergistic/ potentiating drug needed Others, specify_____
Ineffective drug product/ Improper drug Selection	More effective alternative drug is available Condition is already refractory to drug Dosage form is inappropriate The drug is not effective for condition Others, specify_____
Sub therapeutic dosage	Wrong dose (too small) of the drug Frequency is inappropriate (long) Duration of drug use is too short
Supra therapeutic dosage	Wrong dose (too high) of the drug Frequency is inappropriate (short) Duration of drug use is too long Others, specify_____
Adverse drug reaction	Undesired effect from the drug is found Unsafe drug for patient is existed Dosage is administered or changed too rapidly Allergic reactions is found/reported Contraindication to the drug is present Administered too rapidly
Drug interactions	There is (are) Major drug interaction (s)
Failure to receive drugs	Does not understand instructions: the patient does not understand how to properly take or use the drug product and dosage regimen. Patient prefers not to take Patient forgets to take Drug product not available Cost of medication too expensive Cannot swallow/administer drug No willingness to take the drug Unavailability of medication Disbelieves on the drug effectiveness Patient felt better or worse Fear of adverse events Regimen complexity

Medication classes	Individual drugs	Types of DRPs

Annex 4:**የጥናት መረጃ መጠይቅ በአማርኛ (Amharic/Ethiopic version)**

<u>በጥናቱ ለሚሳተፉ ስለጥናቱ ማሳወቅ</u>

የጥናቱ ዋና ተመራማሪ፡መላት በለጠ ደምሴ

የጥናቱዓላማበመድሃኒቶችተያያዝነትባላቸውጉዳዮችለድንገተኛየህክምናአገልግሎትእናተኝቶታካሚ የተዳረጉትንህመማኖችመለየትሲሆንየጥናቱጥቅምለድንገተኛህክምናያደረጉትንከመድሃኒቶችጋርተ ያያዝነትያላቸውንችግሮችመቀነስናበዚህምክንያትየሚመጣውንህመምናሞትመቀነስነው።ስለሆነም እርስዎለዚህጥናትቃለመጠየቅእንዲደረግለዎትተመርጠዋል።ለቃለ-መጠይቁምከ20እስከ30ደቂቃይወስዳሉ፤ጥናቱሲሰራምሆነሲጠየቁስምዎአይጠቀስም፤ቃለመጠይቁን ሲያደርጉበሙሉፍቃደኝነትተመስርተውነው፤ካልፈለጉመተውይችላሉ፤በዚህተሳትፎምንምአይነትየ ተለየጥቅም፣አገልግሎትወይምክፍያአይኖርም።

<u>በጥናቱለሚሳተፉየፍቃደኝነትማረጋገጫ</u>

እኔለዚህጥናትሙሉበሙሉተነግሮኝተረድቻለሁ።አላማውምተኝቶታካሚዎቺንምንያክሉበመድሃ ኒትአጠቃቀምችግርለዚህእንደተዳረጉመገምገምእናመለየትነው።ይህተሳትፎበፈቃደኝነትላይየተ መሰረተመሆኑንተረድቻለሁ።በተጨማሪምየተረዳሁትበዚህተሳትፎአገኛለሁየምለውምንምዓይነ ትየተለየአገልግሎት፤ክፍያወይምስጦታእንደማይኖርተረድቻለሁ።ይህውልየሚያገለግለውለዚህ ጥናትብቻነው።ከዚህበታችስሜየተገለፀውበዚህጥናት ለመሳተፍተስማምቼለሁ።

ስም ፊርማ ቀን

1. **ተሳታፊ፤** _____ _____ _____
2. **መረጃሰብሳቢ ስም ፊርማ ቀን**

_____ _____ _____

3. **የጥናቱዋናተመራማሪ፤መላትበለጠደምሴ**

ለተሳትፎዎአመሰግናለሁ።!

ሀ.የታካሚዎችማህበረሰባዊባህርያቶችመረጃመሰብሰቢያቅጽ(መመሪያ፡ለመረጡትምላሽ የ X ምልክትንያድርጉ)

ካርድቁ_____*የተኙበትቀንከሆስፒታልየወጡበትቀን.....*

1.እድሜ፤_____	2.ፆታ፤	ወንድሴ☐ ☐	እርጉዝ: አዎአይደ☐	☐
3.የጋብቻሁኔታ፤	ያላገባ/ች☐ ያገባ/ች ☐ አግብቶ/ታየፈታ/ችማ☐፤/በሟየሞተችበት/ባት ☐			
4. እምነት	ኦርቶዶክስ☐	መሰለም☐	ፕሮቴስታንት ☐	ካቶሊክ ☐	ሌሎችይገለጽ ☐
5.የትምህርትሁኔታ፤	መጻፍናማንብብአይችሉም ☐ መጻፍናማንበብይችላሉ ☐ አንደኛደረጃ (1ኛ-8ኛ) ☐		ሁለተኛደረጃ (9ኛ-12ኛ) ☐ ☐ ኮሌጅዲፕሎማ ☐ ዩኒቨርስቲዲግሪእናከዛበላይ ☐	
6.አሁንየሚኖሩበት	ከተማአ.አ ☐ ከአ.አውጭ/ክፍለሀገር_____			
7. የሥራሁኔታ፤የመንግስትሰራተኛጡረታ☐ራየሌለው/የለ☐ ☐ የግል መ/ቤት ሰራተኛ☐እስራ ገበሬነጋዴ☐ንሰራ☐ቤትእመ☐ትሌላ ☐ ☐				
8.ሲጋራያጨሳሉ?	አላጭስም ☐ አዎ ☐		ድሮአጭስነበርአሁንግንአቁሜለሁ ☐	
9.መጠጥ(አልኮል) ይጠጣሉ?	አልጠጣም/☐ ☐		ድሮእጠጣነበርአሁንግንአቁሜለሁ ☐	
መልስዎአዎከሆነ፤መጠኑበቀን_____			ለስንትዓመት_____	

10. የአካልእንቅስቃሴ	የእግርጉዞያዘወትራሉ?	አላደርግም አዎ ☐	መልስዎአዎከሆነበቀንለም ንያህልግዜይንዛሉ?	ከ30 ደቂቃበላይ ☐ ከ 30 ደቂቃ በታች☐
	የአካልብቃት/ስፖርትያዘወትራሉ?	አላደርግም☐ አዎ ☐	መልስዎ አዎ ከሆነ በሳምንት ለምን ያህል ጊዜ ይሰራሉ?	በየቀኑ/ ሣምንትሙሉ ☐ 3-6ቀናት ☐ 1-2ቀናት ☐

1.የህመሙ ስም/ስሞች፡- ለምንያክልጊዜ ……..	
2.ተጨማሪ ህመም	ካለ ይገለፅ
3.አሁን ከዚህ ከመግባትዎ በፊት ሲወስዱት የነበሩ መድሀኒቶች	በቁጥር…… ዝርዝር(ስም፣መጠን፣ዝግጅት፣አወሳሰድ፤ለምን ያክል ጊዜ የሚሉት ይገለፁ፤
4.ለአሁኑ ተኚቶ መታከም የዳረገዎት የቱ ይመስለዎታል ሀ. የመድሀኒት አወሳሰድ ችግር/ማቋረጥ ወይም አለመውሰድ አዎአይደለም ☐ ☐ ለ. በወሰድኩት መድሃኒት/ቶች የጎንዮሽ ጉዳት አዎ ☐ አይደለም ☐ ሐ.በሌሎች /መድሃኒትቢጠቀሙም መሻሻል አለው ☐ውም ☐	ተራ ፊደል “ሀ” ላይ መልሱ አዎ ከሆነ በምን ምክንያት እነደሆነ ጠይቁ …….. የ “ለ” መልስዎ አዎ ከሆነ መድሀኒቱ እና የጎንዮሽ ጉዳቱ ይገለፅ ……..
5. የባህልእናያለሀኪምትእዛዝመድኃኒትይወስዳሉ?	በፍጹም ☐ አዎ፤ ☐ አዎከሆነይገለፅ_____

ለ.ለመድኃኒትዎበአግባብአለመውሰድምክንያትሊሆኑየሚችሉ(ከታችከተዘረዘሩትከአንድበላይመምረጥይቻላል)

1. የመድኃኒትዋጋውድነት ----------አዎ□አይደለም□
2. የመድኃኒትበቂአቅርቦትአለመኖር----------አዎ□አይደለም□
3. የመድኃኒቱየጎንዮሽጉዳትፍርሀት----------አዎ□አይደለም□
4. የመድኃኒቱአወሳሰድዘዴከባድነትእናብዙዓይነትመድኃኒትበመሆኑ----------አዎ□አይደለም□
5. የመድኃኒቱአወሳሰድየግዜሰሌዳአለመመቻቸት----------አዎ□አይደለም□
6. ስለበሽታውእናመድኃኒቱበቂየሆነየምክርአልግሎትአለማግኘት----------አዎ□አይደለም□
7. ያለምንምምክንያትበመርሳትብቻ----------አዎ□አይደለም□
8. የመድኃኒትፈዋሽነትአለመተማመን/አለማመን ----------አዎ□አይደለም□

9. መድኃኒትላለመውሰድመምረጥ----------አዎ□አይደለም□

10. ህመሙሲሻሉትወይምሲብስቦት----------አዎ□አይደለም□

11. በስራጫናምክንያትየሚወሰድበትሰዓትማሳለፍእናመተው----------አዎ□አይደለም□

12. በያምምክንያትሰዓቱንጠብቆአለመውሰድ----------አዎ□አይደለም□

13. ሌሎች_____

መ.ከመድኃኒትየተያያዙየጎንዮሽጉዳትወይምየሰውነትቁጣግምገማበተመለከተ

ı. ከባለፈውዓመትወዲህያለውግዜከሚወስዷቸውመድኃኒትበተያየዘያልተለመደ/ያልተፈለገሁኔታ/የጎንዮሽጉዳት/ የሰውነትመቆጣትአጋጥሞትያውቃል?

አዎ□አይደለም□፤መልስዎአዎከሆነየመድኃኒቱዓይነትእናየሁኔታውምልክትይግለጽ፡

2. የጥያቄቁጥር 1 መልስዎአዎከሆነ፤ለሚከተሉትጥያቄዎችመልስይስጡ

2.ı. ጉዳቱ/ቁጣውመድሐኒቱንከወሰዱበኋላነውየተከሰተው?----------አዎ□አይደለም□አይታወቅም□

2.2. መድኃኒቱካቋረጡትበኋላጉዳቱቀንሷል/ቁሟል? ----------አዎ□አይደለም□አይታወቅም□

2.3. መድኃኒቱእንደገናሲወስዱትምልክቱ/ጉዳቱእንደገናተከስቷል------አዎ□አይደለም□አይታወቅም□

2.4. ከመድኃኒቱውጭሌላእንደዚህዓይነትጉዳት/ቁጣሊያመጣየሚችልአለ?-------አዎ□አይደለም□አይታወቅም□

2.5. ጉዳቱየመድኃኒቱመጠንሲጨምርብሷልወይምመጠኑሲቀንስቀንሷል? -------አዎ□አይደለም□አይታወቅም