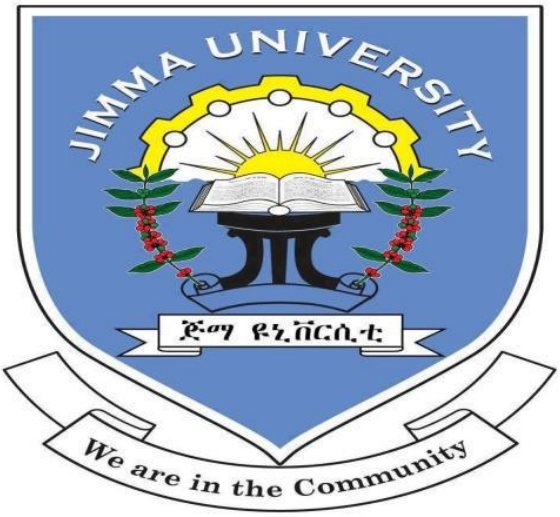
Adverse Drug Events and Contributing Factors among Hospitalized Adult Patients at Jimma Medical Center, South West Ethiopia: A Prospective Observational Study



By: Tamiru Sahilu (B. Pharm.)

A Research Thesis to be Submitted to Institute of Health, School of Pharmacy, Jimma University, in Partial Fulfillment of the Requirements of the Masters of Science Degree in Clinical Pharmacy

January, 2020

Jimma, Ethiopia

JIMMA UNIVERSITY

INSTITUTE OF HEALTH

SCHOOL OF PHARMACY

Adverse Drug Events and Contributing Factors among Hospitalized Adult Patients at Jimma Medical Center, South West Ethiopia: A Prospective Observational Study

By: Tamiru Sahilu (B. Pharm.)

Advisors:

1. Mrs. Mestawet Getachew (B.Pharm, Msc in Clinical pharmacy)
2. Mr. Tsegaye Melaku (B.Pharm, MSc, Assistant Professor of Clinical Pharmacy)

January, 2020

Jimma, Ethiopia

Abstract

Background: Adverse drug events are an important source of morbidity and mortality in different clinical settings of different countries. It causes a negative impact on patient's health status that leads to a major impact on expenditure of healthcare systems. Knowledge of the incidence, type, and preventability of adverse drug events is core to develop prevention strategy; as a result to improve the quality of health care delivery and relevant to minimize the expenditure of health care cost.

Objective: To assess burden of adverse drug events and contributing factors among hospitalized adult patients at Jimma Medical Center.

Methods: A prospective observational study was conducted. Data was collected from all patients admitted from April 15 to July 15, 2019 at medical ward and who fulfilled the inclusion criteria. Data was checked for consistency and analyzed using statistical software package, SPSS version 24. Statistical significance was considered at p-value <0.05.

Results: A total of 319 patients with 5667 person-days were followed. One hundred sixteen adverse drug events were identified with incidence of 36.36 (95% CI 30.05- 43.61) per 100 admissions (crude rate), 20.47 (95% CI 16.91- 24.55) per 1000 person days and 8.32 (95% CI 6.87- 9.97) per 100 medication orders. Causality were 26.72% definite, 60.34% probable, 12.93% possible ADEs. Regarding the severity, 37.07% mild, 52.59% moderate and 10.34% were severe ADEs. Most (62.07%) of ADEs were definitely/probably preventable. Anti TB agents, disease of circulatory system, disease of digestive system, being on medication during admission and length of hospital stay ≥15 days were independent predictors of the occurrence of ADEs. A total of 94 potential ADEs were identified with incidence of 29.47 (95% CI 23.8- 36.06) per 100 admissions (crude rate), 16.59 (95% CI 13.55- 20.3) per 1000 person days and 6.74 (95% CI 5.45- 8.25) per 100 medication orders. Number of medications ≥7, antiviral agents, anti-seizures, anti TB agents and anticoagulants were independent predictors of potential ADEs.

Conclusion: The incidence of ADEs identified in this study was consistent with published data. One in every four patients admitted in the ward experienced ADEs during their hospital stay and about two out of three cases were judged as either moderate or severe. About two third of the identified ADEs were deemed probably or definitely preventable.

Recommendations: Close monitoring and multidisciplinary communication on use of high-risk medications such as anti TB, antiviral agents, anti-seizures and anticoagulants.

Keywords: Adverse drug events, potential adverse drug events, incidence, predictors, factors, Ethiopia.

Acknowledgement

I would like to express my deepest gratitude to my advisors Mrs. Mestawet Getachew and Mr. Tsegaye Melaku for providing me guidance and constructive idea from the beginning in preparation of this research thesis.

Also, I would like to acknowledge Jimma University for funding the study, Jimma Medical Center and study participants for their co-operation. Furthermore, my friends and data collectors would be appropriately acknowledged for their invaluable contribution in this study.

Table of Contents

Contents

List of Figures

List of Tables

Abbreviation and Acronyms

ACE	Angiotensin-converting enzyme
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AOR	Adjusted odds ratio
AUROC	Area under receiver operating characteristic
AZT	Zidovudine
BUN	Blood urea nitrogen
$FeS0_4$	Ferrous sulphate
GTT	Global Trigger Tool
HMG CoA	Hydroxy methyl glutaryl coenzyme A
ICU	Intensive care unit
IHI	Institute for Healthcare Improvement
INH	Isoniazid
JMC	Jimma Medical Center
LOS	Length of Stay
MAEs	Medication Administration Errors
MEs	Medication Errors
NCCMERP	National Coordinating Council for Medication error Reporting and Prevention
NSAIDs	Non-steroidal anti-inflammatory drugs
PTU	Propylthiouracil
RH	Rifampicin, Isoniazid

RHZE	Rifampicin, Isoniazid, pyrazinamide, ethambutol
SJS	Stevens Johnson syndrome
TEN	Toxic epidermal necrosis
TNF-α	Tumor necrosis factor-alpha
UFH	Unfractionated heparin
WHO	World health organization

1. INTRODUCTION

1.1. Background

Adverse drug events (ADEs) are any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it. ADEs include side effects, ADR and medication error (1, 2). Institute of Medicine defined ADEs as an injury resulting from medical intervention related to a drug. This includes medication errors, adverse drug reactions, allergic reactions, and overdoses (3).

Hospital adverse events are an important source of morbidity and mortality in different countries and settings (4, 5) and represent an important item of expenditure for healthcare systems and their prevention could be associated with a relevant cost saving (6). ADEs are among the leading causes of morbidity and hospitalization (7). In study done across low and middle income countries, the rate of adverse events was around 8%, of which 83% could have been prevented and 30% led to death (8). In other studies ADE, preventability ranges 14.2% - 92.9% (9-12). A systematic review done by Mekonnen *et al* (13) revealed 43.5% of ADEs were deemed preventable in African Hospitals.

National Coordinating Council for Medication Error Reporting and Prevention defines medication error as ‘‘any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional and patient’’ (14). Medication errors are a major health burden contributing to 18.7% - 56% of all ADEs among hospitalized patients (15). Globally, the cost associated with medication errors has been estimated 42 billion dollars annually, not counting lost wages, productivity, or health care costs (8).

The systematic review done by Jolivot *et al* (16) reported that the incidence of ADEs in adult inpatients ranged from 0.37 to 27.4%. In meta-analysis, pooled estimate from nine articles showed the prevalence of inpatient ADEs were 21.6% (17). In other review, prevalence of ADE ranges 4.5% to 34.1% in adults (18).

Prospective cohort study done in four Saudi Arabia hospitals showed the incidence of ADEs was 6.1 per 100 admissions (19). The rate of ADEs ranges from 16.3 to 18.3 per 100 patients (20-22) and 7.9 to 30.6 per 1000 patient-days (19, 23), with potential ADE of 9.4 per 100 patient-years (24).

Evidences showed that ADEs caused 1.4% life-threatening harm, 28% serious harm (25), 96% temporary harm, 4% complications (26), and patient death of 1326-1433 in a year (mortality rate 8.81- 9.52 cases per 100,000 patients) (27).

A review of articles by Zhou *et al* (7), identified risk factors for adverse drug events and grouped them into five main categories: patient-, disease-, medication-, health service- and genetics-related. Among these, medication- and disease-related risk factors were most frequently studied. Polypharmacy (28), length of hospital stay (29), comorbidity (30), inappropriate use of drugs, cardiovascular agents, and anti-infective (7) were identified significantly associated risk factors for ADE. Age > 65 years old, receiving more than five drugs, and starting new high-risk drugs were found having significant relationships with preventable ADEs (31).

1.2. Statement of the problem

ADEs are an important cause of morbidity and mortality worldwide and represent a substantial burden on healthcare delivery systems. It is associated with healthcare costs due to hospital admissions, prolonged length of stay, as well as additional interventions (32, 33). However, there is little data available from low- and middle-income countries.

In Africa, hospital-acquired adverse drug reactions (ADRs) incidence reported was 25%, of which 44% was serious possible ADRs (34). The median percentage of patients experienced any suspected ADE at hospital admission was 8.4%, while ADE causing admissions were reported 2.8% of patients. A median of 43.5% of the ADEs were deemed preventable. The median mortality rate attributed to ADEs was reported to be 0.1% (13).

Treatments with six or more drugs during hospitalization, prior 3 months hospitalization, comorbidity and traditional medicine use during preadmission were found the risk factors for hospital-acquired drug reactions. Polypharmacy on admission also increased the risk of ADEs and preventable ADEs. Preventable ADEs were associated with more severe harm than non-preventable ADEs. Compared with rest of the world, drug reaction reports were more often reported for patients 18-44 years old in sub Saharan Africa (29, 34-36).

In sub-Saharan Africa, 9% of reported drug reactions were for cardio metabolic drugs (ant diabetic, antithrombotic and cardiovascular), in rest of the world for 18%. Most reports were for drugs acting on the renin-angiotensin system (36% sub-Saharan Africa and 14% rest of the world). Anticoagulants and anti- diabetic agents result in most of ADEs. Anticoagulant and ant-diabetic ADEs added greater than 65% to inpatient costs (35, 37).

ADEs in hospitals have additional healthcare cost, an average increase of length of stay (LOS) of 1.7 - 3.1 days and increased risk of death (1.9 times higher than those not experiencing an ADE) Preventable ADEs have higher costs and increase length of stay of 3.37 days. The severity of the ADE was also associated with higher costs (38, 39).

The estimated ADE rate during hospitalization was 4.2 events per 100 admissions. In addition, 3.2% of admissions were caused by ADEs. Fifteen percent of hospital ADEs and 76% of ADEs causing admission were judged preventable (40).

Preventable adverse drug reactions occurring in inpatients, ranged from 0.006 to 13.3 per 100 patients. Preventable drug reaction incidence varied significantly with event detection method (prospective > retrospective > voluntary reporting methods), hospital setting (ICU >wards), and medical discipline (medical > surgical wards) (41).

In Morocco, among the 52 medication errors, 53.8% led to potential ADEs and 46.2% led to actual preventable ADEs. There were 7.7 medication errors for 1000 patient-days. The preventable ADEs occurred in the prescribing (71.1%), administration (21.2%), transcription (5.7%), and dispensing stages (42).

The incidence of medication error in Ethiopia was found to be 56.4% (43). At Northwest part of Ethiopia, the estimated medication error reporting was found to be 29.1%. The perceived rates of medication administration errors reporting for non-intravenous related medications were ranged from 16.8 to 28.6 % and for intravenous-related from 20.6 to 33.4 % (44).

In Ethiopia, to the best of our knowledge, Berhe *et al* (45) and Angamo *et al* (46) have addressed this issues. But, evidences related to incidence, preventability and severity of ADEs in inpatients are scarce.

1.3. Significance of the study

This study will contribute knowledge to health care professionals and health care system to have a better understanding of the common ADEs and their contributing factors for better management and prevention. Thus, a better understanding of contributing factors for ADEs may enhance the application of prevention for those patients at risk. Thus reducing ADEs is expected to result in safer health care services, reduced health care costs, and improved health outcomes. In addition, result from this study will contribute knowledge to growing body of literature documenting in the area of ADEs. Furthermore, the finding of this study will be a baseline to perform further studies in the area of ADEs.

2. LITERATURE REVIEW

2.1. Incidence and responsible drugs of ADEs

A systematic review of prospective studies in Indian Hospitals showed the median incidence of ADRs that lead to hospitalization and that developed during hospitalization were 2.85% and 6.34% respectively. High incidence rate was found with studies conducted in intensive care units, elderly age groups, with intensive monitoring, duration of greater than one year and multidisciplinary team. The fatal ADR incidence was 0.08% (47).

Four classes of drugs most frequently suspected in admissions due to ADRs were anti-infective agents (40.92%) including anti-tubercular drugs (13.15%), steroids (14.03%), anti-coagulants (8.77%), and NSAIDs (7.89%) (48).

The prevalence of ADRs in adult population in Singapore was 12.4% at admission and ADRs causing admission were 8.1%. The most common ADRs were gastrointestinal-related, while the most common drug category causing ADRs were cardiovascular drugs. Patients with ADRs had a longer length of stay than those who did not (49).

The main class of products in African individual case safety report (spontaneous reports to WHO database) are nucleotide reverse transcriptase inhibitors (14.04%), nonnucleoside reverse transcriptase inhibitors (9.09%), combinations of sulfonamides and trimethoprim (2.98%) and angiotensin-converting enzyme (ACE) inhibitors (2.42%). While the main product classes implicated in individual case safety report from the rest of the world are tumor necrosis factor-α (TNF-α) inhibitors (5.29%), topical non-steroidal anti-inflammatory preparations (2.26%), selective immune suppressants (2.08%), selective serotonin reuptake inhibitors (2.04%) and HMG CoA reductase inhibitors (1.85 %) (50).

The leading ADRs causal drugs according to therapeutic class were anti-infective (17%), cardiovascular (17%), antineoplastic (15%), and analgesics/anti-inflammatory agents (15%). The organ systems most often affected were gastrointestinal (24%), dermatologic (19%), and immune systems (15%) (51).

Study done at four Hospitals in South Africa, reported 8.4% ADR-related admissions and it was associated with female sex, increasing drug count, increasing comorbidity score and use of antiretroviral therapy (52).

Study done in Lagos State University Teaching Hospital Lagos, Nigeria the number of patients who experienced ADRs was 67 (n = 624, 10.7%). The incidence rate of ADRs was 10.7 per 100 patients' population. Mostly implicated classes of drugs were anti-diabetics (26.7%) and NSAIDs (29.3%) (53).

The prevalence of ADEs in a general teaching hospital in Rabat, Morocco performed among the 1390 patients surveyed, 59 (4.2%) experienced at least 1 ADE and for 20 patients (1.4%) the ADE was responsible for hospitalization or prolongation of hospitalization. The ADE was classified as serious in 28 patients. Of the total of 76 ADEs, 10 (13.2%) were categorized as preventable; 6 of these occurred during the treatment monitoring phase. Patients who experienced an ADE were more likely to be women, to be younger (< 30 years) and to be hospitalized in medical departments (54).

Prospective cohort multicenter study in seven intensive care units in academic and military hospital of Rabat, Morocco showed of the 696 patients studied, and the investigators identified 108 incidents of ADEs (15.5 %). The reviewers concluded that 56 (70%) of 80 ADEs were non preventable (42).

In Ugandan inpatients the incidence of possible hospital-acquired suspected ADRs was 25%, of which 44% experienced serious possible ADRs. The risk of probable ADRs was 11%, of which 46% had serious probable ADRs. Antibacterial (51/194), cardiovascular drugs (16/194), anti-malarias (12/194) and analgesics (10/194) were the most frequently implicated (34)

At four hospitals in South Africa, ADRs contributed to the death of 2.9% of medical admissions and of 357 (n=56, 16%) deaths were ADR-related. Tenofovir, rifampicin and co-trimoxazole were the most commonly implicated drugs. Forty three percent of ADRs were considered preventable. And HIV-infected patients on antiretroviral therapy, exposure to more than seven drugs and increasing comorbidity score were independently associated with ADR-related death (55).

A prospective cross-sectional study conducted by Angamo *et al* (46) showed 10.3% of patients had ADR-related hospitalization to JMC (Jimma Medical Center) the then so called Jimma University Specialized Hospital.

2.2. Medication error and potential ADEs

The incidence of medication errors was higher in medical care units than in acute and nursing care units (40.9, 15.6, and 17.4 per 1000 patient-days, respectively). The monitoring and ordering stages were the most common error stages (39 % and 34 % of all medication errors, respectively). Non-psychiatric drugs were three times as likely to cause ADEs with errors compared to psychiatric drugs (25). Seventy-one percent of the serious medication errors occurred at the prescribing stage of the medication-use process (40).

In a Moroccan medical intensive care unit (ICU) Jennane *et al* (56) found 492 medication errors (MEs), which incidence was 10 per 100 orders and 967 per 1000 patient-days. There were 113 potential ADEs (2.28 per 100 orders and 222 per 1000 patient-days) and 8 ADEs (0.16 per 100 orders and 15.7 per 1000 patient-days). MEs occurred in transcribing stage in 60% cases. Antibiotics were the drug category in 33%. Two ADEs conducted to death.

In a tertiary hospital in southwestern Nigeria, the total prescribing error rate was 40.9% with 1.3% being clinically serious. Omitting to write an ending date or duration for therapy and unsafe abbreviations were the most common errors. Prescriptions involving antimicrobials produced the bulk of errant prescriptions (57, 58).

In Sudan, 12.2% of prescriptions contained errors being potentially serious to the patients and 17.8% showed errors of major importance (59).

In Egypt, medication administration errors in a University Hospital study included 237 patients and 28 nurses. A total of 5531 errors were observed with an average number of 2.67 errors per observation. More than 85% of the observations had at least one error, and the overall error rate was 37.68%. The highest error rate was detected in injections especially the intravenous route (39.58%) (60).

In public hospitals in the Gauteng Province of South Africa, 296 medication errors were identified, of which most were wrong-time errors and omissions (61).

The incidence of medication administration error among nurses in Ethiopia was 56.4%. The majority (87.5 %) of the medications have documentation error, followed by technique error (73.1 %) and time error (53.6 %) (43).

In the medical ICU of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, about 220 patient charts were reviewed with a total of 1311 patient-days, and 882 prescription episodes. Three hundred fifty nine MEs were detected; with prevalence of 40 per 100 orders. Common prescribing errors were omission errors 154 (42.89%), 101 (28.13%) wrong combination, 48 (13.37%) wrong abbreviation, 30 (8.36%) wrong dose, wrong frequency 18 (5.01%) and wrong indications 8 (2.23%) (62).

The prevalence of medication prescribing errors in the ICU of Jimma Medical Center was 209/398 (52.5%). Common prescribing errors were using the wrong combinations of drugs (25.7%), wrong frequency (15.5%), and wrong dose (15.1%). Errors associated with antibiotics represented a major part of the medication prescribing errors (32.5%) (63). Prevalence of medication administration errors was 51.8%. Common administration errors were attributed to wrong timing (30.3%), omission due to unavailability (29.0%) and missed doses (18.3%) among others (64).

2.3. Contributing factors of ADEs

Retrospective record review undertaken on 463 records in university hospital in Finland identified the risk of ADEs increased with the length of hospital stay and the increased number of drugs patients used. The patients with coronary diseases had a 2.5 times higher risk of experiencing ADEs. In addition, the risk of ADEs during hospitalization increased together with the co-morbidity of patients (29).

Case-control study done on 20,628 patients 65years and older presenting to the emergency department in Taiwan revealed independent risk factors for ADEs included number of medications and increased concentration of serum creatinine (65).

A systematic review of prospective studies in Indian Hospitals reported important risk factors for ADRs included elderly, female sex and polypharmacy. The hospitalized patients have a significant burden of ADRs (47).

A meta-analysis on 5367 inpatients from four studies reported Patients aged ≥ 77 years experienced more ADEs and preventable ADEs compared with patients aged ≤52 years. The top five high risk drugs were antibiotics, sedatives, anticoagulants, diuretics and antihypertensives (36).

2.4. Methods used for detecting ADEs and potential ADEs

Methods for detecting adverse drug events (ADEs) include voluntary reporting, chart review, computerized surveillance, and direct observation (66). Each method detects different types of ADEs, and no single detection method is considered a gold standard for identifying ADEs. Medical record or chart review is a more systematic method for identifying ADEs, detecting many more ADEs compared with voluntary reporting and computerized surveillance (67). The use of multiple detection methods cause greater increases in the ADR reporting rates than single (68, 69).

Medication-related harm can be detected using the adverse drug event trigger tool (70) and the medication module of the Global Trigger Tool (GTT) (71) developed by the Institute for Healthcare Improvement (IHI). The use of an ADE trigger tool and medication module of the global trigger tool can facilitate manual chart reviews and increase detection of ADEs (72).

2.5. Conceptual Framework

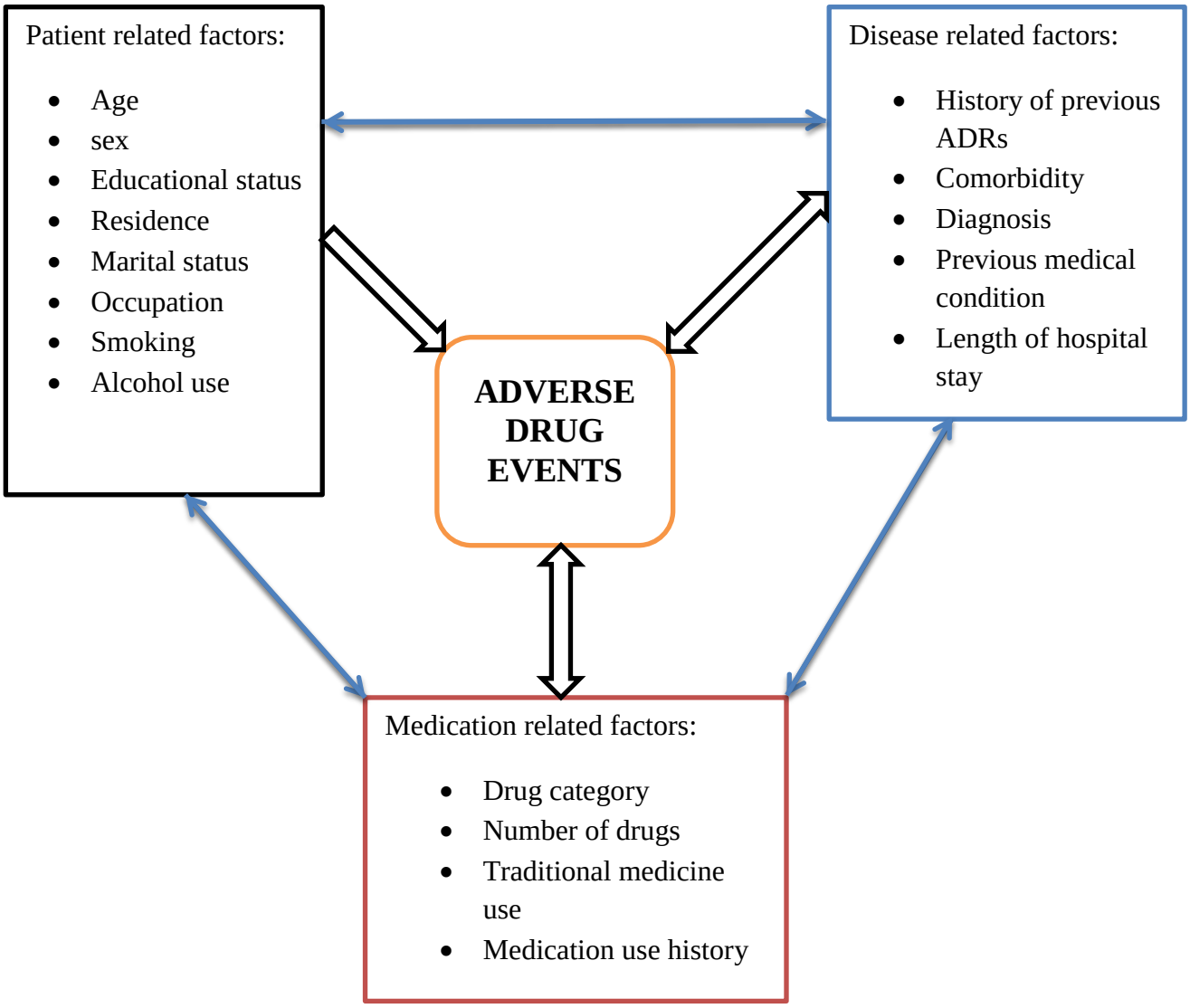


Figure 1. Conceptual framework for the study at JMC, 2019.

3. OBJECTIVES

3.1. General objective

To assess burden of adverse drug events and contributing factors among hospitalized adult patients at Jimma Medical Center.

3.2. Specific objectives

- To assess the incidence of adverse drug events
- To identify types of adverse drug events in terms of severity and preventability
- To determine contributing factors for adverse drug events

4. METHODS AND MATERIALS

4.1. Study area and period

Study was conducted from April 15 to July 15, 2019 at JMC, located 352km south-west of Addis Ababa, the capital city of Ethiopia. JMC is the only medical center in south-west Ethiopia with 800 active beds. It has the catchment population of over 15 million. The hospital service is rendered with more than 2000 permanent staffs (both technical and administrative). It serves more than 400,000 patients per year at emergency, outpatient departments, and various inpatient wards. Among the wards, medical ward has different units i.e. cardiac, neurology, pulmonology, general ward, ICU and TB unit.

4.2. Study Design

Prospective observational study was carried out at medical ward of JMC.

4.3. Population

4.3.1. Source Population:

All patients who were admitted to medical ward of JMC.

4.3.2. Study Population:

All adult patients, who were admitted during the study period and fulfilled the inclusion criteria.

4.3.2.1. Inclusion criteria

- Patients who were admitted to medical ward of JMC with in the study period.
- Patients whose age ≥18 years
- Patients taking at least one medication after admission and/or continued at least one medication from previous regimen
- Patients who were willing to participate
- Patients who stayed greater than 24hrs in hospital

4.3.2.2. Exclusion criteria

- Patients who had incomplete medical and medication records.
- Unconscious patients

4.4. Sample size and sampling technique

The Sample size was calculated by using single population proportion formula based on the following assumption: Z = $(1.96)^2$, the proportion (P) = 0.525 taken from study done by Agalu *et al* (64) and marginal error (d) = 5%, the sample size n = 384.

$$n = \frac{Z_{\frac{\alpha}{2}}^{2} P (1 - P)}{d^2}$$

The number of study population (N) in the study setting i.e the number of patients admitted to the medical ward of JMC from September 2018 to February 2019 (6 months period) taken from admission/discharge registry of the hospital is 1171 patients. The size of the population is less than 10,000. Therefore; the sample size were corrected using the following correction formula (73).

$$\text{Corrected sample size} = \frac{\text{n x N}}{n+N}$$

The calculated sample size; by using the above correction formula is 289.2~ 290. Whereas: n- is the non-corrected sample size which is 384. N is the size of the study population which can be admitted within 6 months, which is 1171. By adding 10% for non-responders:

The final sample size = 319

Consecutive type of sampling technique was used to collect data from all patients who fulfilled the inclusion criteria.

4.5. Data collection Instrument and procedures

Standardized semi structured questionnaire was used. The questionnaire was translated into two common local languages (Afan Oromo and Amharic) to solicit information from patients. Data was taken from patient medical charts, patient interview and direct observation. A standard questionnaire (Annex I) was designed by reviewing different literatures for important variables (70, 74-76). Adverse drug event Trigger tool (70) and medication module of the Institute for Healthcare Improvement (IHI) global trigger tool (71) for measuring ADEs developed by the IHI

was used to facilitate manual chart reviews and increase detection of ADEs (annex II). The preventability of ADE was assessed using modified Schumock and Thornton's criteria (77). ADE causality was assessed by Naranjo algorithm (78).

4.6. Study variables

4.6.1. Dependent variables

Primary outcome:

- Adverse drug events

4.6.2. Independent variables

Patient related:

- Age
- Sex
- Educational status
- Residence
- Marital status
- Occupation
- Smoking
- Alcohol use

Disease related:

- History of previous ADRs
- Comorbidity
- Diagnosis
- Length of hospital stay
- Previous medical condition

Medication related:

- Drug category
- Number of drugs
- Traditional medicine use
- Medication history

4.7. Data quality assurance and management

A standard questionnaire was designed by reviewing different literature. Experts from clinical pharmacy evaluated and assured the data collection form was comprehensive enough to collect all the information intended to address the purpose and goals of the study. Then pretest was done

on 5% of sample size and appropriate changes were made such as previous medical condition and number of medication at admission was added. Training for data collectors (pharmacists and nurse), regular supervision and daily checkup of filled data were done to improve quality of the study.

Before data exporting to SPSS for analysis, data was cleared and checked for completeness in EpiData. Any erroneous, ambiguous and incomplete data was excluded.

4.8. Data processing and analysis

All collected patient's data was entered into EpiData version 4.4.1 and exported to SPSS version 24 for clearing and analysis, respectively. The data was analyzed by SPSS version 24. Stata version 15.1 was used to calculate incidence of ADEs.

Frequency of Socio demographic characteristics, clinical characteristics, diagnosis, medication ordered, previous medical condition and medication history were calculated. Categorical variables were described as numbers and percentages, and continuous variables as mean ± standard deviation (SD).

All variables were tested for multi-colinearity by collinearity diagnostics and variables with variance inflation factor greater than 10 were removed. Assumption of independence (adequacy of cells) was carried out by chi square and only variables not violating the assumption were analyzed by logistic regression. All variables were tested for an association with ADE in univariate logistic regression. Those variables demonstrating a univariate association with at least marginal significance ($P<0.25$) were included in a multivariate regression. Multivariate logistic regression was performed using backward likelihood ratio to identify independent predictors of ADE occurrence. $P<0.05$ were considered for significance. Adjusted odd ratio (AOR) was used as measure strength of association. Finally, the result was presented by using narrative, tables, figures and charts.

4.9. Outcome and Validating Methods

4.9.1. Main outcome measures

The primary outcome of the study was the incidence of ADEs occurring during inpatient stay. The secondary outcome was severity and preventability of ADEs. Multiple detection methods

were employed to identify ADEs in the ward to maximize data yield. Multi-method event detection is recommended (74).

1. Daily chart review for all admissions, the following documents were assessed for ADEs including discharge summary, procedure notes, physician progress notes, laboratory reports, physician orders, nursing /multi-disciplinary progress notes and data about drug exposure (79). During the chart review, trigger tools or 'clues' was used to facilitate ADE detection, because either they are antidotes or given to reverse the action of a drug responsible for adverse drug event (70, 71) (Annex II). The list of laboratory reports reviewed was:

1.1. Liver (Alanine aminotransferase (ALT), aspartate aminotransferase (AST))

1.2. Kidney (Urea, serum creatinine)

1.3. Complete blood count

1.4. Blood glucose

1.5. Serum electrolytes (calcium, potassium, sodium)

1.6. Coagulation profile (prothrombin time, international normalized ratio (INR))

1.7. Electrocardiogram (ECG)

2. Patient observation and interview: For further information or clarification and confirmation of the cases, the patient was interviewed using the questionnaire (Annex I) and observed for harms.

3. Attendance at multidisciplinary ward rounds: For further evaluation and confirmation of cases especially on the exclusion of possible disease condition role in doubtful cases.

4. Voluntary reports from staff: All medical ward staff were informed about the study and invited to inform the principal investigator any incident that they noted during their daily activities. Systematic approach recommended by Tangiisuran *et al* (80), case identification, confirmation by a reviewer and classification of incidents was applied to ensure the correct classification and to avoid inclusion of any doubtful cases which could overestimate the incidence of ADEs (**figure 2**).

Patient identification and recruitment

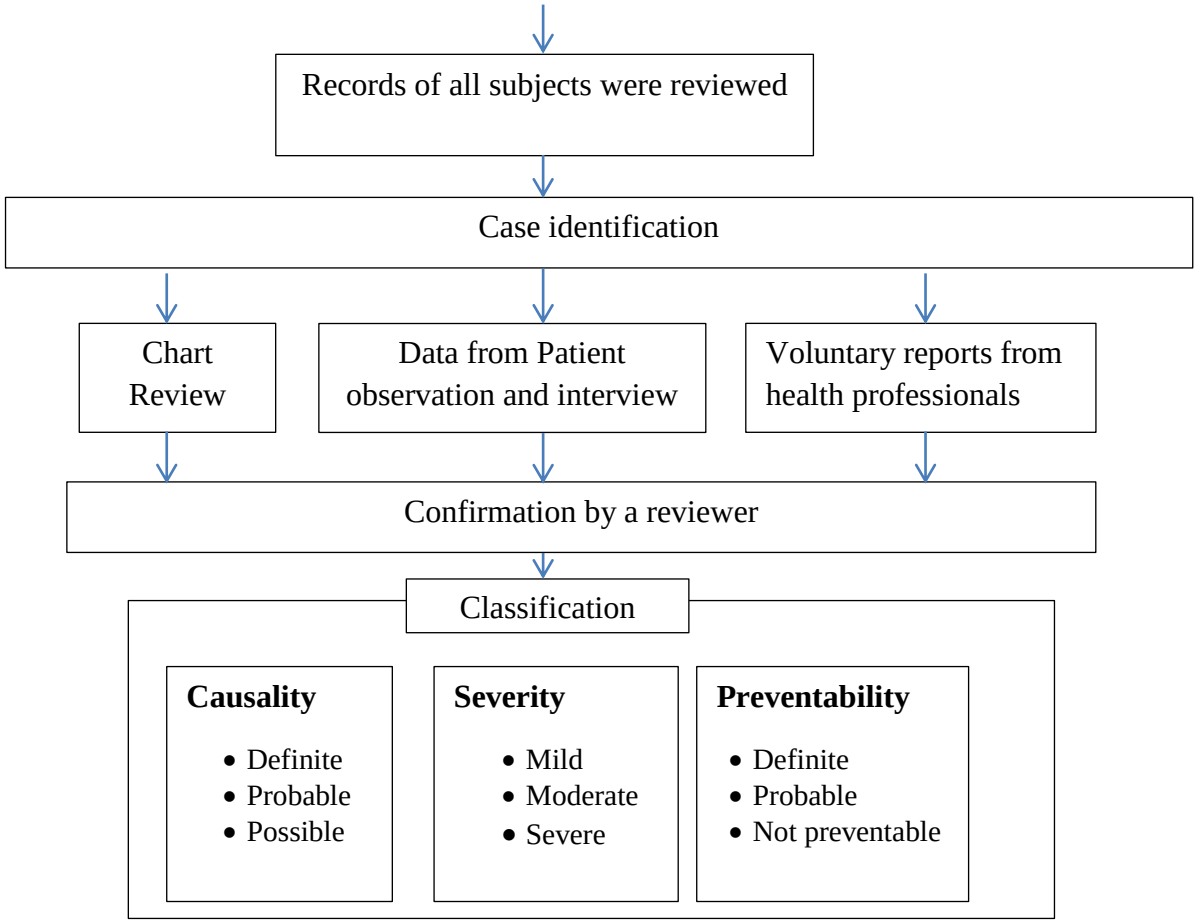


Figure 2: Flow diagram of methods employed in identifying ADEs

When suspected ADEs identified based up on the above detection methods, the principal investigator further evaluated its relationship with the medication using Naranjo causality assessment algorithm (78) (Annex III). Only those in the category of definite, probable and possible were considered. During this evaluation, the expertise of the ward team was contacted when required for further evaluation especially on the exclusion of possible disease condition role in ADE. The severity of the incidents was categorized as modified Hartwig ADR severity assessment scale (81). ADEs preventability was assessed using modified Schumock and Thornton's criteria (77).

Potential ADEs were identified on the conditions that medication error with the potential to cause an injury (75). Drug- drug interaction was assessed as per Lexicomp® drug interaction classification, since Lexicomp Interactions scored highest in scope and in completeness compared to seven drug information resources including Micromedex Drug Interactions (82).

Potential ADEs were categorized based up on NCCMERP severity category (74, 76) (**Table 1**) and according to the stage in the medication use process they have occurred as prescribing, dispensing, administering, transcribing and monitoring (74, 75).

Table 1: NCC MERP severity category modified definition

NCC MERP severity category		NCC MERP severity category modified definition
No harm	B	An event occurred but the medication did not reach the patient (an 'error of omission' does reach the patient).
	C	An event occurred that reached the patient, but did not cause harm.
	D	An event occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.
Harm	E	An event occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.
	F	An event occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.
	G	An event occurred that may have contributed to or resulted in permanent patient harm.
	H	An event occurred that required intervention necessary to sustain life.
Death	I	An event occurred that may have contributed to or resulted in the patient's death.

Analysis of outcomes includes ADEs incidence per 100 admissions, per 1000 patient-days, and per 100 medication orders; severity of ADEs; percentage of ADEs that is preventable, non-preventable; medication use process stages (ordering/prescribing, transcribing, dispensing, administering, or monitoring) of the medication management process during which the medication error responsible for ADEs.

The incidence of ADEs were calculated by Stata version 15.1 as (70):

A. ADEs incidence per 100 admissions:

- The total number of ADEs identified, divided by the total number of admissions; multiplied by 100.

B. ADEs incidence per 1000 patient-days:

- The total number of ADEs identified, divided by the total number of patient- days multiplied by 1,000

C. ADEs incidence per 100 medication orders:

- The total number of ADEs identified, divided by sum of medications ordered multiplied by 100

4.10. Ethical consideration

Before the commencement of the study, ethics approval was obtained from the Institutional Review Board, Jimma University. The hospital director and head of the Department of internal medicine was informed about the purpose of the study to get agreement and co-operation. Participants were informed about the purpose/nature of the study prior to the data collection and approved invitation by written informed consent. The participants' information was kept confidential. The adverse drug events identified during the data collection were handled by the investigator to protect the patient from any potential risks or harms.

4.11. Limitation of the study

According to Naranjo causality assessment algorithm, detection of blood, urine, tissue or other specimen concentrations of the medicine is applied to see whether the concentration of the medication is in the accepted toxic or supra-therapeutic range and administration of placebo to see reappearance of the adverse event, to ascertain ADE causality in addition to other scores. But, these are not performed in our setting, which overestimate or underestimate the scores.

4.12. Dissemination plan

The final result of the study will be disseminated to responsible bodies such as school of Pharmacy of Jimma University, JMC and Ethiopian Food and Drug Administration (EFDA). Attempts will be made to present the finding on national Professional associations such as Ethiopian Pharmacists Association (EPA) and Ethiopian Public Health Association (EPHA) and

international scientific conferences. Finally, the study finding will be submitted to reputable professional journal for publication so as to serve as base line for further studies.

4.13. Operational definitions and definition of terms

Medication errors: Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional and patient (2, 14).

Adverse drug events: Adverse drug events (ADEs) are any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it. ADEs include side effects, ADR and medication error(1).

Adverse drug reactions: A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (2).

Potential ADE: A medication error with the potential to cause an injury but which does not actually cause any injury, either because of specific circumstances, chance, or because the error is intercepted and corrected (75).

Harm: Temporary or permanent impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting from requiring intervention (76).

Adverse drug event triggers: a medication, laboratory value, or other indicator that prompts further review of patient care for the purpose of uncovering adverse drug events that may otherwise go undetected or unreported (83).

Incident: an event or circumstance which could have, or did lead to unintended and/or unnecessary harm to a person, and/or a complaint, loss or damage (83).

Educated: Participants who had primary, secondary or tertiary education.

5. RESULTS

5.1. Study population characteristics

During the 3 months study period, a total of 612 patients were assessed for eligibility at medical ward of JMC. Of these, 319 patients were followed daily until discharge and included in analysis (**figure 3**).

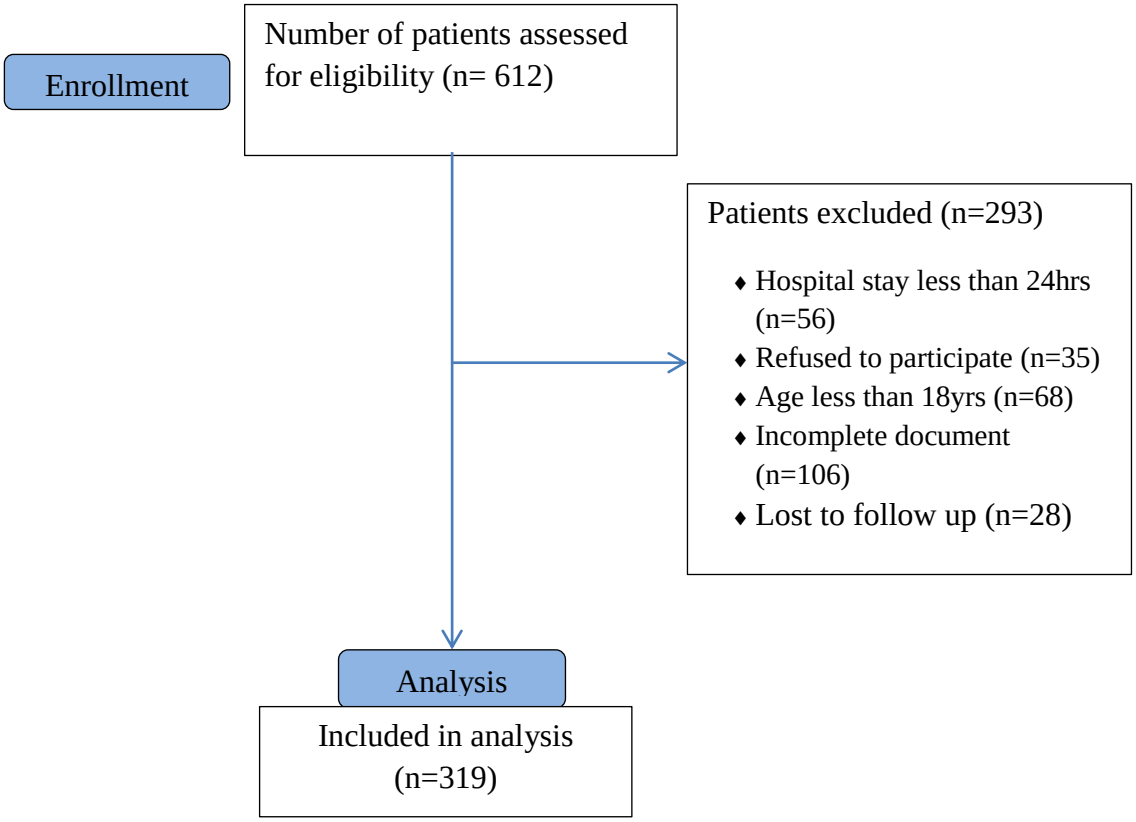


Figure 3: Flow chart showing the number of study participants at JMC, April 15- July 15, 2019

5.2. Socio-demographic characteristics of study population

From a total of 319 participants, 161 (50.5%) were females, 123 (38.6%) were with in age group of 18-35 years. The mean ± SD age of the participants was 43±17.6 years. Most of the participants, 225 (70.5%) were from rural area, 213 (66.8%) were married, 218 (68.3%) were uneducated, 155 (48.6%) were farmers, 87 (27.3%) participants drink alcohol, 26 (8.2%) were smokers (**Table 2**).

Table 2: Socio demographic characteristics of study participants at JMC, April 15- July 15, 2019

Variables		Frequency n=319	Percentage
Sex	Male	158	49.5
	Female	161	50.5
Age, years	Mean ± SD	43 ± 17.6	
	Median (IQR)	43 (27-55)	
	18-35	123	38.6
	36-50	92	28.8
	51-65	67	21.0
	≥66	37	11.6
Residence	Rural	225	70.5
	Urban	94	29.5
Marital status	Married	213	66.8
	single	87	27.3
	widowed	9	2.8
	Divorced	10	3.1
Educational status	Uneducated	218	68.3
	Educated	101	31.7
Occupation	Student	51	16.0
	Government employee	13	4.1

	Merchant	23	7.2
	Self employed	21	6.6
	Farmer	155	48.6
	Unemployed	56	17.6
Alcohol use	Yes	87	27.3
	No	232	72.7
Tobacco smoking status	Yes	26	8.2
	No	293	91.8

5.3. Clinical characteristics of study population

Of 319 patients, 76 (23.8%) had history of hospitalization in previous 3 months before the study period, 11 (3.4%) patients had history of ADRs and 14 (4.4%) patients had used traditional medicine. The mean ± SD and total length of hospital stay of the patients was 17.8 ± 14.5 days and 5667 patient-days respectively. Comorbidities were determined by charlson's comorbidity index (CCI) weight and the mean ± SD of CCI was 2.8 ± 2.3. The mean ± SD number of medications ordered for the patient was 4.4 ± 2 and most of the patients, 155 (48.6%) was on 4-6 drugs (**Table 3**).

Table 3: Clinical characteristics of study participants at JMC, April 15- July 15, 2019

Variables		Frequency n=319	Percentage
Number of medications	Mean ± SD	4.4 ± 2	
	1-3	121	37.9
	4-6	155	48.6
	≥7	43	13.5
Traditional medicine use	Yes	14	4.4
	No	305	95.6
History of ADR	Yes	11	3.4
	No	308	96.6
History of Hospitalization in the previous 3 months	Yes	76	23.8
	No	243	76.2

Length of hospital stay, days	Mean ± SD	17.8 ± 14.5
Comorbidities (Charlson comorbidity Index)	mean ± SD	2.8 ± 2.3

The diagnosis of the patients were categorized according to international classification of disease (ICD) 10 code. One patient can have more than one diagnosis and most of the patients were diagnosed diseases of the circulatory system 169 (53%), infectious and parasitic diseases 110 (34.5%), diseases of the genitourinary system 91 (28.5%), diseases of the blood and immune mechanism 86 (27%), endocrine, nutritional and metabolic diseases 69 (21.6%), diseases of the nervous system 64 (20.1) and disease of the digestive system 63 (19.7%) (**Table 4**).

Table 4: Diagnosis of study participants at JMC, April 15- July 15, 2019

ICD-10 Code	Diagnosis	Frequency (%) n=319
I00-I99	Diseases of the circulatory system	169 (53.0)
A00-B99	Infectious and parasitic diseases	110 (34.5)
N00-N99	Diseases of the genitourinary system	91 (28.5)
D50-D89	Diseases of the blood and immune mechanism	86 (27.0)
E00-E89	Endocrine, nutritional and metabolic diseases	69 (21.6)
G00-G99	Diseases of the nervous system	64 (20.1)
K00-K95	Disease of the digestive system	63 (19.7)
J00-J99	Diseases of the respiratory system	62 (19.4)
C00-D49	Neoplasms	7 (2.2)
L00-L99	Diseases of the skin and subcutaneous tissue	5 (1.6)
S00-T88	Injury and other external causes	3 (0.9)
F01-F99	Mental and Neurodevelopmental disorders	1 (0.3)

A total of 1395 medications were ordered for the patients. Medications were categorized according to anatomical and therapeutic classification (ATC). Most of the patients received antibiotics (50.8%), cardiovascular medicines (48.3%), gastrointestinal medicines (35.7%) and analgesics (28.2%) (**Table 5**).

Table 5: Medication ordered for study participants at JMC, April 15- July 15, 2019

Medication ordered	Frequency (%) n=319
Antibiotics	162 (50.8)
Cardiovascular medicines	154 (48.3)
Gastrointestinal medicines	114 (35.7)
Analgesics	90 (28.2)
Vitamins and antianemic agents	78 (24.5)
Electrolytes	59 (18.5)
Antiplatelates	54 (16.9)
Antidyslipidemic agents	53 (16.6)
Anticoagulants	52 (16.3)
Antituberculosis	43 (13.5)
Steroids	38 (11.9)
Antidiabetics	27 (8.5)
Antiseizures	22 (6.9)
Antivirals	21 (6.6)
Antifungals	12 (3.8)
Antiasthmatics	11 (3.4)
Anti-thyroid agents	9 (2.8)
Antipsychotics	9 (2.8)
Antimalarials	6 (1.9)
Antihistamines	3 (0.9)

Based on documented and available data, 166 (52%) patients had history of medication use in previous 3 months before the study period. One hundred eight (33.86%) patients were on medication during admission; 23 (21.29%) patients were on ≥ 3 drugs. Most of the patients were on Cardiovascular medicines 79 (73.15%), antibiotics 28 (25.93%) and antiviral agents 28 (25.93%) (**Table 6**).

Table 6: Medication history of the study participants at JMC, April 15- July 15, 2019

Medication history	Frequency (%) n=319
History of Medication use in the past 3 months	166 (52)
Number of medication on admission	
1-2 drugs	85 (78.7)
≥3 drugs	23 (21.3)
Medications by class (n= 108)	
Cardiovascular medicines	79 (73.15)
Antibiotics	28 (25.93)
Antivirals	28 (25.93)
Antituberculosis	11 (10.19)
Antiplatelates	11 (10.19)
Antidyslipidemic agents	10 (9.26)
Antiasthmatics	10 (9.26)
GI medicines	9 (8.33)
Steroids	7 (6.48)
Antimalarials	6 (5.56)
Anticoagulants	5 (4.63)
Antianemic agents	5 (4.63)
Antiseizures	5 (4.63)
Antipsychotics	4 (3.70)
Analgesics	3 (2.78)
Anti-thyroid agents	2 (1.85)
Number of medication on admission	
1-2 drugs	85 (26.65)
≥3 drugs	23 (7.2)

Among patients involved in the study, 171 (53.6%) patients had previous medical condition. Diseases of the circulatory system 88 (51.46%), infectious and parasitic diseases 48 (28.07%) and endocrine, nutritional and metabolic diseases 25 (14.62%) were the common previous medical condition of the patients (**Table 7**).

Table 7: Previous medical condition of the study participants at JMC, April 15- July 15, 2019

ICD-10 Code	Diagnosis	Frequency (%)
	Patients with previous medical condition (n=319)	171 (53.6)
By category (n= 171)		
I00-I99	Diseases of the circulatory system	88 (51.46)
A00-B99	Infectious and parasitic diseases	48 (28.07)
E00-E89	Endocrine, nutritional and metabolic diseases	25 (14.62)
J00-J99	Diseases of the respiratory system	14 (8.18)
N00-N99	Diseases of the genitourinary system	12 (7.02)
D50-D89	Diseases of the blood and immune mechanism	7 (4.09)
K00-K95	Disease of the digestive system	5 (4.63)
G00-G99	Diseases of the nervous system	5 (4.63)
C00-D49	Neoplasms	2 (1.17)

5.4. Incidence of ADEs

A total of 116 ADEs were identified during the 3 months study period. In total, 85 patients (26.65%) accounted for these ADEs. Twenty two patients were found to have more than 1 ADEs. The incidence of ADEs were 36.36 (95% CI 30.05- 43.61) per 100 admissions (crude rate), 20.47 (95% CI 16.91- 24.55) per 1000 person days and 8.32 (95% CI 6.87- 9.97) per 100 medication orders.

Of 116 ADEs identified, 42 (36.23%) occurred with medication error. The stage of medication use process at which medication error occurred was at prescribing stage 37 (88.1%) and at monitoring stage 5 (11.9%) (**figure 4**).

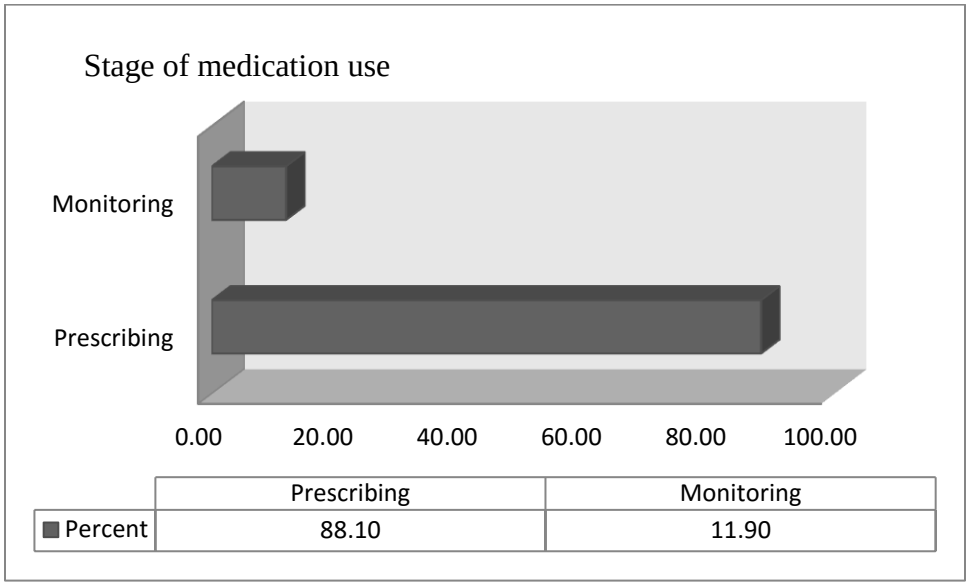


Figure 4: Stages of medication use process at which ADEs occurred with medication error, study at JMC, April 15- July 15, 2019.

The causal relationship between ADEs and an administered drug was established by Naranjo algorithm following the instructions (Annex III). For each ADE, the algorithm was done and 31(26.72%) ADEs occurrence were definite, 70 (60.34%) ADEs were probable, 15 (12.93%) were possible ADEs (**Figure 5**).

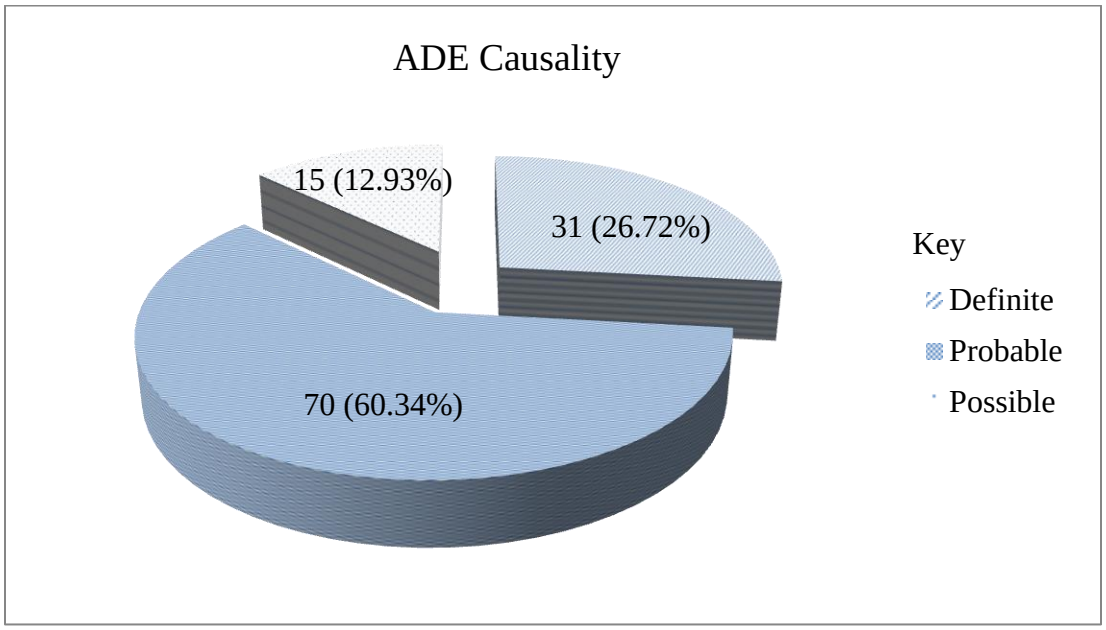


Figure 5: Result of Naranjo causality Assessment Algorithm for the study participants at JMC, April 15- July, 2019.

Adverse drug events were categorized according to system organ affected by ADEs. The most common system organs affected were gastrointestinal system 35 (30.17%), endocrine and metabolic 25 (21.55%), hematologic 15 (12.93%) and cardiovascular system 23 (19.83%). Hypotension 18 (15.52%), hypokalemia 11 (9.5%), vomiting 11 (9.5%), hepatotoxicity 8 (6.9%) and dyspepsia 7 (6%) were some of the commonly encountered ADEs (**Table 8**).

Table 8: ADE classification by system organ class, JMC, April 15- July, 2019.

System organ class	Frequency (%)	ADEs n (%)	Medication involved (n)
Gastrointestinal system	35 (30.17)	Constipation 4 (3.5)	Metoprolol tartarate(1) morphine (1) (enalapril+ UFH+omeprazole (1)) Furosemide (1)
		Diarrhea 2 (1.7)	Metronidazole (1) warfarin+FeS04 (1)
		dyspepsia 7 (6)	RHZE (4) Salbutamol (1) RH (1) Warfarin+UFH (1)
		GI ulcer 1 (0.9)	Aspirin (1)
		Hepatotoxicity 8 (6.9)	RHZ (8)
		Vomiting 11 (9.5)	Warfarin (1) ceftriaxone (3) cimetidine (1) Enalapril (1) Furosemide (1) RHZE (3) Warfarin+UFH (1)
		Nausea 1 (0.9)	Warfarin (1)
		Upper GI bleeding 1 (0.9)	Furosemide (1)
Endocrine and metabolic	25 (21.55)	hyperkalemia 4 (3.5)	UFH (1) Enalapril (1) Spironolactone (1) propranolol (1)
		Hypocalcemia 2 (1.7)	Furosemide (2)
		Hypoglycemia 2 (1.7)	Insulin (1) (ceftriaxone+vancomycin (1))
		hypokalemia 11 (9.5)	Furosemide (3) prednisolone (1) RHZE (1) insulin (5) Gentamicin (1)
		hyponatremia 5 (4.3)	Furosemide (4) RHZE (1)
		Hyperglycemia 1 (0.9)	Dexamethasone (1)
Cardiovascular System	23 (19.83)	Hypotension 18 (15.52)	Furosemide (14) Mannitol (1) Metoprolol succinate (1) chlorpromazine (1) cimetidine(1)
		2nd degree AV block 1 (0.9)	Digoxin (1)
		Cardiogenic shock 1 (0.9)	Furosemide + Enalapril + Metoprolol succinate (1)
		hypovolemic shock 1 (0.9)	Furosemide (1)
		peripheral edema 1 (0.9)	Amlodipine (1)
		Tachycardia 1 (0.9)	Salbutamol (1)

Hematologic	15 (12.93)	Anemia 5 (4.3)	Cotrimoxazole (2) RH (1) Furosemide (1) Cotrimoxazole+AZT (1)
		pancytopenia 3 (2.6)	Phenobarbital (1) chlorpromazine (1) cotrimoxazole+ AZT (1)
		Thrombocytopenia 2 (1.7)	Amlodipine (1) UFH (1)
		Bicytopenia (Plt + RBC) 1 (0.9)	PTU (1)
		Bleeding 4 (3.5)	Warfarin (3) (Warfarin + UFH (1))
Neuromuscular and skeletal system	5 (4.31)	Peripheral neuropathy 5 (4.3)	INH (5)
Dermatologic	4 (3.45)	skin rash 2 (1.7)	Cotrimoxazole (1) Vancomycin (1)
		TEN with SJS overlap 1 (0.9)	Loratadine (1)
		Toxic epidermal necrosis (TEN) 1 (0.9)	Ivermectin (1)
Genitourinary system	4 (3.45)	increased BUN 1 (0.9)	Cotrimoxazole (1)
		Acute kidney injury 3 (2.6)	Enalapril (2) Gentamicin (1)
Central nervous system	3 (2.59)	headache 3 (2.6)	cimetidine (1), (enalapril+Furosemide+ ceftriaxone (1)), (Warfarin+UFH (1))
Respiratory system	1 (0.86)	Dry cough 1 (0.9)	Enalapril (1)
Immune system	1 (0.86)	Allergy 1 (0.9)	Cotrimoxazole (1)
Total	116 (100%)	116 (100%)	

The common medication classes accountable for development of ADEs were diuretics 27 (26.47%), antibiotics 17 (16.67), anti TB 15 (14.71%), cardiovascular medicines 11 (10.78%), anticoagulants 9 (8.82%) and antidiabetic agents 6 (5.88%). Furosemide 25 (24.5%), RHZE 9 (8.82%), ceftriaxone 7 (6.86%), enalapril 6 (5.88%), cotrimoxazole 6 (5.88%) and insulin 6 (5.88%) were the mostly involved medications (**Table 9**).

Table 9: Medications accountable for ADEs, JMC, April 15- July, 2019.

Medication class	Frequency (%)	Medications involved (n)
Diuretics	27 (26.47)	Furosemide (25) Mannitol (1) Spironolactone (1)
Antibiotics	17 (16.67)	Cotrimoxazole (6) Gentamicin (1) Metronidazole (1) ceftriaxone (7) Vancomycin (2)
Anti TB	15 (14.71)	RH (1) RHZE (9) INH (5)
Cardiovascular medicines	11 (10.78)	Metoprolol tartarate(1) Digoxin (1) Metoprolol succinate (2) Enalapril (6) propranolol (1)
Anticoagulants	9 (8.82)	UFH (4) Warfarin (5)
Antidiabetic	6 (5.88)	Insulin (6)
GI medicines	3 (2.94)	Cimetidine (2) omeprazole (1)
Antivirals	2 (1.96)	AZT (2)
Steroids	2 (1.96)	Prednisolone (1) Dexamethasone (1)
Antipsychotic Medicines	1 (0.98)	Chlorpromazine (1)
Antihypertensive	1 (0.98)	Amlodipine
Anti-asthmatics	1 (0.98)	Salbutamol
Anti-seizures	1 (0.98)	Phenobarbital
Antithyroid Agents	1 (0.98)	PTU
Analgesics	1 (0.98)	Morphine
Anti-anemic agents	1 (0.98)	FeS04
Antiplatelates	1 (0.98)	Aspirin
Antihistamines	1 (0.98)	Loratadine
Anthelmintics	1 (0.98)	Ivermectin
Total	102 (100)	

Interventions were given to 88 (75.86%) ADEs. No intervention was given for the rest 28 (24.14%) ADEs. There was one or more interventions for one ADE and of total ADEs intervened, 39 (44.32%) ADEs were treated with medication. For 34 (38.64%) ADEs the suspected medication were discontinued, for 19 (21.59%) ADEs additional laboratory or vital sign monitoring were performed, 15 (17.05%) ADEs were treated with an antidote and for 7 (7.95%) ADEs the suspected medication dose was changed (**Table 10**).

The time to development of ADEs was calculated using Kaplan Meier. The mean onset of ADEs was 9.95±1.06 days (95% CI 7.875- 12.031). The median onset of ADEs was 8±0.57 days (95% CI 6.888- 9.112). Fifty seven (49.14%) ADEs appeared with in first week, 41 (35.34%) ADEs appeared with in second week, 10 (8.62%) ADEs appeared with in third week and 8 (6.9%) ADEs appeared after 22 days of the patients started their medication (**Table 10**).

Table 10: Treatment, outcome and time for onset of ADEs, study at JMC, April 15- July, 2019.

	Frequency	Percent
Treatment of ADE		
Yes	88	75.9
No	28	24.1
Interventions		
Antidote	15	17.0
Medication dose changed	7	8.0
Medication discontinued	34	38.6
Required increased monitoring	19	21.6
Required treatment	39	44.3
Time for onset of ADEs (in days)		
Mean	9.95 (95% CI: 7.88-12.03)	
Median	8 (95%CI: 6.89- 9.11)	
1-7 days	57	49.1
8-14 days	41	35.3
15-21 days	10	8.6
≥22 days	8	6.9

5.5. Severity of ADEs

According to modified Hartwig severity Assessment Scale (Annex V), 61 (52.59%) were moderate, 43 (37.07%) were mild and 12 (10.34%) were severe in category (**Figure 6**).

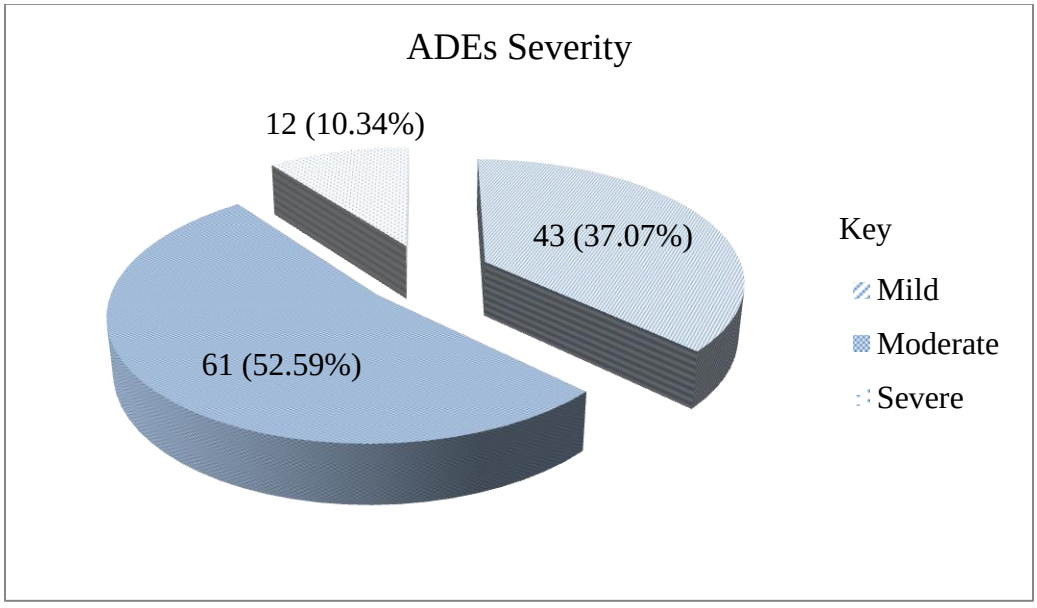


Figure 6: Modified Hartwig ADEs Severity category, study at JMC, April 15- July, 2019.

In terms of system organ, dermatologic 2 (50%), endocrine and metabolic 4 (16%), hematologic 1(6.7%) and gastrointestinal (GI) system 5 (14.3%) were the severe occurrences of ADEs. The rest were mild and moderate ADEs (**figure 7**).

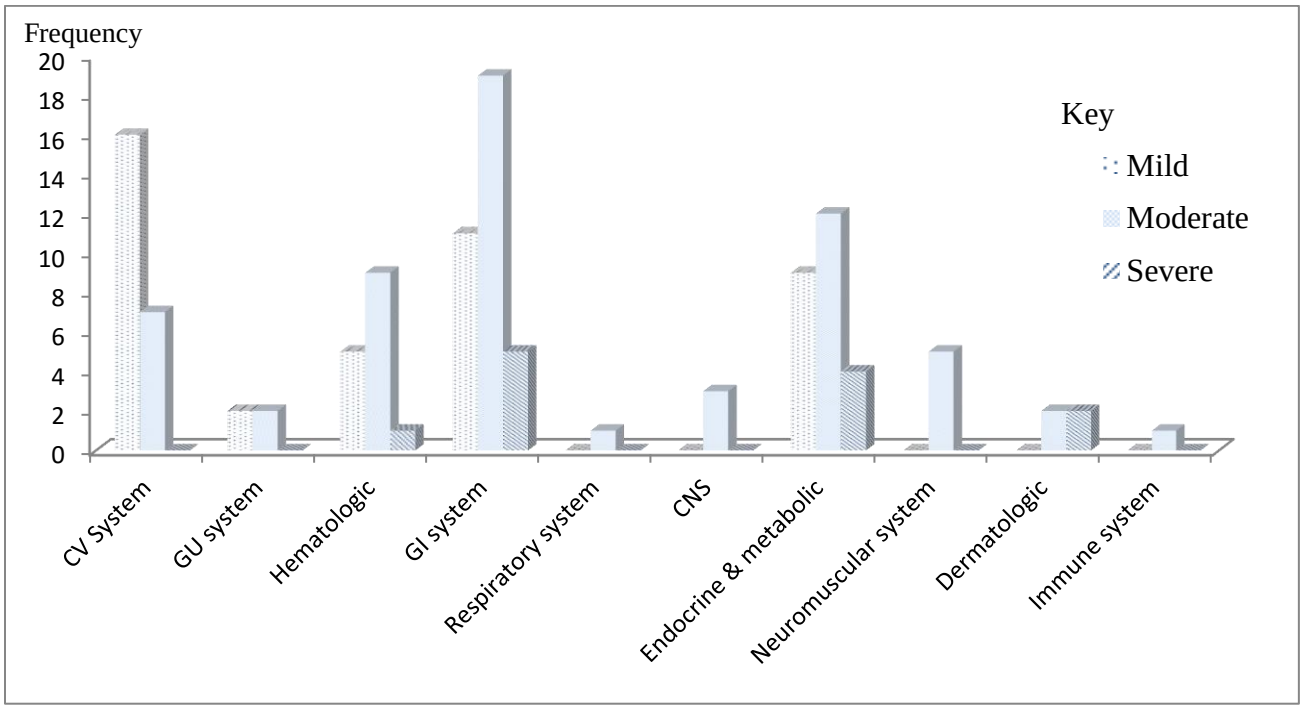


Figure 7: Severity of ADEs in terms of system organ, study at JMC, April 15- July, 2019.

5.6. Preventability of ADEs

Preventability of ADEs was assessed by modified Schumock and Thornton's preventability criteria (Annex IV). Thirty one (26.72%) were definitely preventable, 41 (35.35%) were probably preventable and 44 (37.93%) were non-preventable ADEs (**Figure 8**).

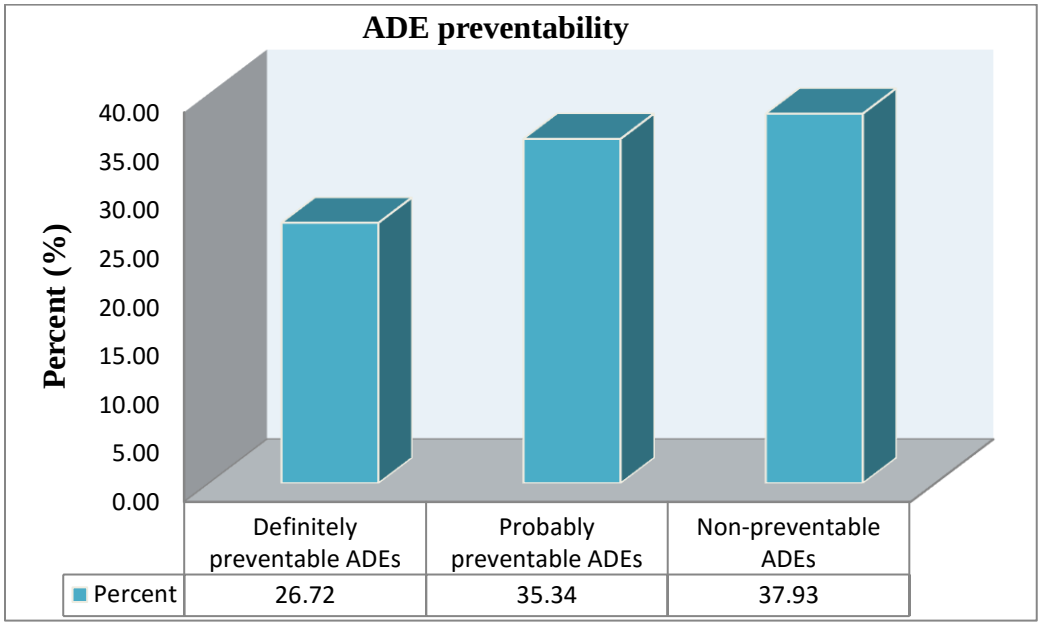
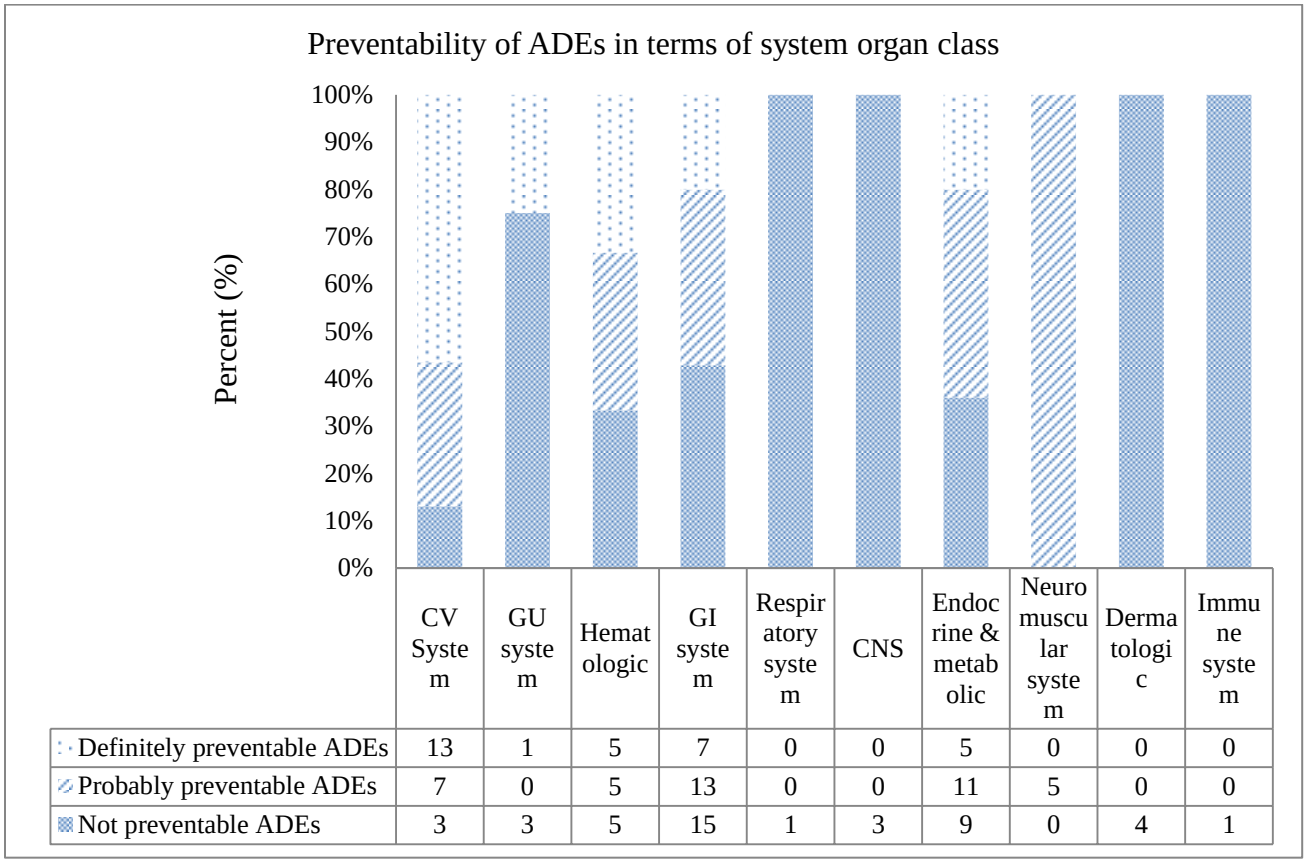


Figure 8: Preventability of ADEs, study at JMC, April 15- July 15, 2019.

In terms of system organ classes, the definitely/probably preventable ADEs were cardiovascular (CV) system 20 (27.78%), genitourinary (GU) system 1 (1.39%), hematologic 10 (13.89%), gastrointestinal (GI) system 20 (27.78%), endocrine and metabolic 16 (22.22%) and neuromuscular and skeletal system 5 (6.94%). The rest were non preventable ADEs (**figure 9**).



	CV System	GU system	Hematologic	GI system	Respiratory system	CNS	Endocrine & metabolic	Neuromuscular system	Dermatologic	Immune system
Definitely preventable ADEs	13	1	5	7	0	0	5	0	0	0
Probably preventable ADEs	7	0	5	13	0	0	11	5	0	0
Not preventable ADEs	3	3	5	15	1	3	9	0	4	1

Figure 9: Preventability of ADEs in terms of system organ, study at JMC, April 15- July 15, 2019.

5.7. Incidence, severity and preventability of potential ADEs

A total of 94 potential ADEs were identified during the 3 months study period. The incidence of potential ADEs were 29.47 (95% CI 23.8- 36.06) per 100 admissions (crude rate), 16.59 (95% CI 13.55- 20.3) per 1000 person days and 6.74 (95% CI 5.45- 8.25) per 100 medication orders. The stage of medication use process at which potential ADEs occurred was at prescribing stage 63 (67%), at administration stage 16 (17%) and at monitoring stage 15 (16%) (**Figure 10**).

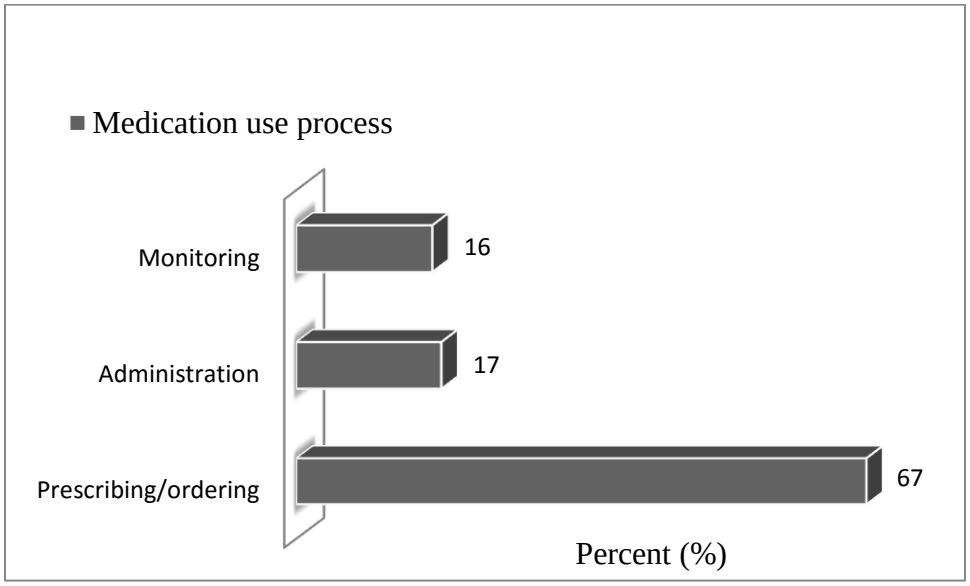


Figure 10: Stages of medication use process at which potential ADEs occurred, study at JMC, April 15- July 15, 2019.

The severity of potential ADEs was assessed by NCC MERP severity category. Accordingly, 73 (77.7%) were category D, 18 (19.2%) were category C and 3 (3.2%) were category B and all were preventable (**Figure 11**).

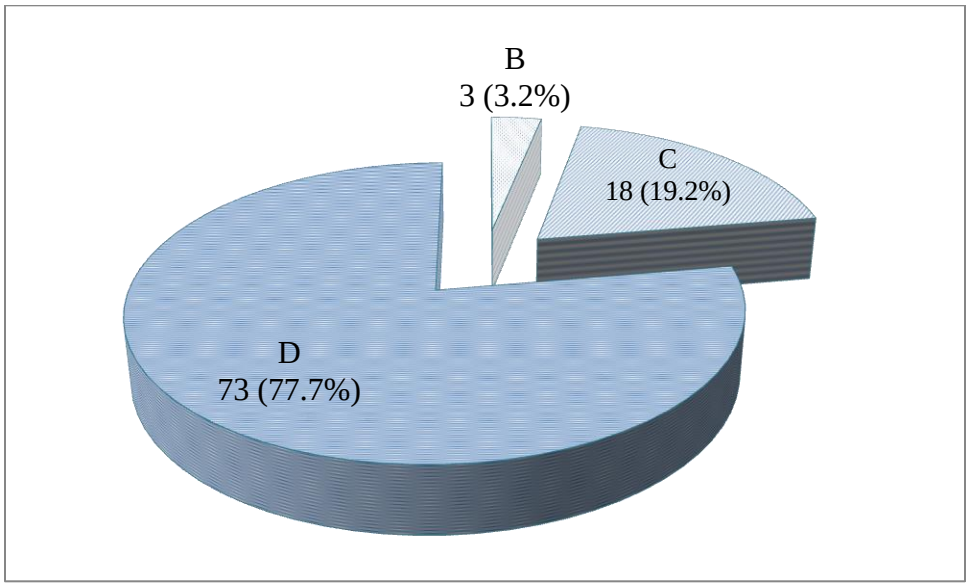


Figure 11: Severity of potential ADEs, study at JMC, April 15- July 15, 2019.

The relationships of identified ADEs and potential ADEs were depicted in **figure 12**. Of 116 ADEs identified, 42 occurred with medication error.

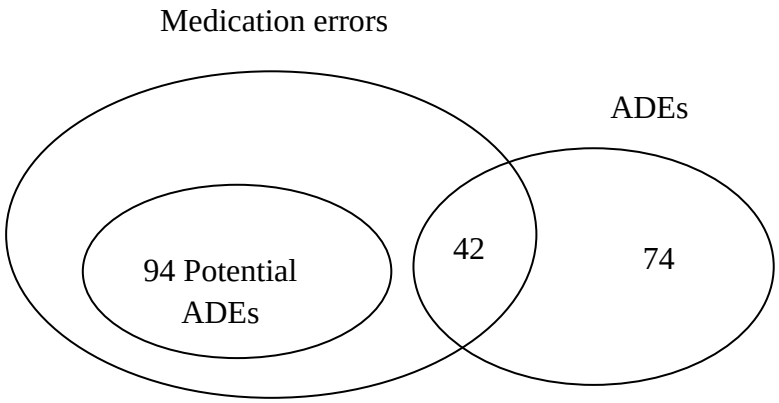


Figure 12: Relationship between ADEs and potential ADEs, April 15- July 15, 2019.

5.10. Factors associated with ADEs

5.10.1. Patient related factors

The association between patient related factors and occurrence of ADEs was analyzed as summarized in **table 11**. In univariate analysis, patients with age range of 51- 65 years had an association with the occurrence of ADEs. Otherwise, there is no significant difference in patient related characteristics (sex, residence, educational status, alcohol consumption, smoking and occupation) between patients who experienced ADEs and patients who didn't experience ADEs.

Table 11: Univariate analysis of Patient related characteristics of study participants at JMC, 2019

Variables		ADE occurrence		Total	COR (95% CI)	P value
		No; n (%)	Yes; n (%)	n (%)		
Sex	Male	116 (36.4)	42 (13.2)	158 (49.5)	1	
	Female	118 (37)	43 (13.5)	161 (50.5)	1.006 (.613- .653)	.98
Residence	Rural	163 (51.1)	62 (19.4)	225 (70.5)	1	
	Urban	71 (22.3)	23 (7.2)	94 (29.5)	.852 (.490-1.482)	.57
Educational status	Uneducated	153 (48)	65 (20.4)	218 (68.3)	1	
	Educated	81 (25.4)	20 (6.3)	101 (31.7)	.581 (.329 -1.027)	.062
Alcohol consumption	No	167 (52.4)	65 (20.4)	232 (72.7)	1	
	Yes	67 (21)	20 (6.3)	87 (27.3)	.767 (.431-1.364)	.366
Tobacco use	No	216 (67.7)	77 (24.1)	293 (91.8)	1	
	Yes	18 (5.6)	8 (2.5)	26 (8.2)	1.247 (.521-2.983)	.620
Age	18 - 35 years	97 (30.4)	26 (8.2)	123 (38.6)	1	
	36 - 50 years	68 (21.3)	24 (7.5)	92 (28.8)	1.317 (.697- 2.486)	.396
	51- 65 years	41 (12.9)	26 (8.2)	67 (21)	2.366 (1.229- 4.55)	.010
	≥ 66 years	28 (8.8)	9 (2.8)	37 (11.6)	1.199 (.504- 2.853)	.681
Occupation	Student	42 (13.2)	9 (2.8)	51 (16)	1	
	Government employee	11 (3.4)	2 (0.6)	13 (4.1)	.848 (.160-4.506)	.847

Merchant	16 (5)	7 (2.2)	23 (7.2)	2.042 (.651-6.405)	.221
Self employed	18 (5.6)	3 (0.9)	21 (6.6)	.778 (.188-3.213)	.728
Farmer	107 (33.5)	48 (15)	155 (48.6)	2.093 (.944-4.642)	.069
Unemployed	40 (12.5)	16 (5)	56 (17.6)	1.867 (.741-4.704)	.186

COR: crude odds ratio, CI: confidence interval

5.10.2. Disease related factors

Patients with digestive system, circulatory system and endocrine and metabolic disease had significant association with occurrence of ADEs. Also the patients' length of hospital stay had significant association with occurrence of ADEs (**Table 12**).

Table 12: Univariate analysis of disease related characteristics of study participants at JMC, 2019

Variables		ADE occurrence		Total	COR (95% CI)	P value
		No; n (%)	Yes; n (%)	n (%)		
Infectious Disease	No	155 (48.6)	54 (16.9)	209 (65.5)	1	
	Yes	79 (24.8)	31 (9.7)	110 (34.5)	1.126 (.671- 1.891)	.653
Genitourinary System	No	166 (52)	62 (19.4)	228 (71.5)	1	
	Yes	68 (21.3)	23 (7.2)	91 (28.5)	.906 (.520- 1.578)	.726
Blood & immune	No	175 (54.9)	58 (18.2)	233 (73)	1	
	Yes	59 (18.5)	27 (8.5)	86 (27)	1.381 (.802- 2.378)	.245
Endocrine and metabolic disease	No	191 (59.9)	59 (18.5)	250 (78.4)	1	
	Yes	43 (13.5)	26 (8.2)	69 (21.6)	1.957 (1.11- 3.453)	.020
Digestive system	No	199 (62.4)	57 (17.9)	256 (80.3)	1	
	Yes	35 (11)	28 (8.8)	63 (19.7)	2.793 (1.568- 4.98)	.000
Respiratory system	No	187 (58.6)	70 (21.9)	257 (80.6)	1	
	Yes	47 (14.7)	15 (4.7)	62 (19.4)	.853 (.448- 1.622)	.627
Nervous system	No	185 (58)	70 (21.9)	255 (79.9)	1	
	Yes	49 (15.4)	15 (4.7)	64 (20.1)	.809 (.426- 1.535)	.517

Circulatory system	No	121 (37.9)	29 (9.1)	150 (47)	1	
	Yes	113 (35.4)	56 (17.6)	169 (53)	2.068 (1.234- 3.47)	.006
LOS	1- 7 days	48 (15)	6 (1.9)	54 (16.9)	1	
	8- 14 days	93 (29.2)	23 (7.2)	116 (36.4)	1.978 (.755- 5.186)	.165
	15-21 days	43 (13.5)	24 (7.5)	67 (21)	4.465 (1.668-11.95)	.003
	≥22 days	50 (15.7)	32 (10)	82 (25.7)	5.120 (1.965-13.34)	.001

COR: crude odds ratio, CI: confidence interval, LOS: length of stay

5.10.3. Drug related factors

Anti TB agents, anti-diabetic agents, gastrointestinal medicines, number of medications the patient was receiving, and medication error were associated with occurrence of ADEs (**Table 13**).

Table 13: Univariate analysis of drug related characteristics of study participants at JMC, 2019

Variables		ADE occurrence		Total	COR (95% CI)	P value
		No; n (%)	Yes; n (%)	n (%)		
Antibiotics	No	114 (35.7)	43 (13.5)	157 (49.2)	1	
	Yes	120 (37.6)	42 (13.2)	162 (50.8)	.928 (.565- 1.525)	.768
Cardiovascular medicines	No	126 (39.5)	39 (12.2)	165 (51.7)	1	
	Yes	108 (33.9)	46 (14.4)	154 (48.3)	1.376 (.836- 2.264)	.209
Antivirals	No	220 (69)	78 (24.5)	298 (93.4)	1	
	Yes	14 (4.4)	7 (2.2)	21 (6.6)	1.410 (.549- 3.622)	.475
Anticoagulants	No	197 (61.8)	70 (21.9)	267 (83.7)	1	
	Yes	37 (11.6)	15 (4.7)	52 (16.3)	1.141 (.590- 2.205)	.695
Anti dyslipidemic agents	No	196 (61.4)	70 (21.9)	266 (83.4)	1	
	Yes	38 (11.9)	15 (4.7)	53 (16.6)	1.105 (.573- 2.132)	.765
Anti TB agents	No	210 (65.8)	66 (20.7)	276 (86.5)	1	
	Yes	24 (7.5)	19 (6)	43 (13.5)	2.519 (1.299- 4.885)	.006

Vitamins and antianeamic	No	181 (56.7)	60 (18.8)	241 (75.5)	1	
	Yes	53 (16.6)	25 (7.8)	78 (24.5)	1.423 (.814- 2.486)	.215
Antidiabetic agents	No	219 (68.7)	73 (22.9)	292 (91.5)	1	
	Yes	15 (4.7)	12 (3.8)	27 (8.5)	2.400 (1.074- 5.363)	.033
Steroids	No	208 (65.2)	73 (22.9)	281 (88.1)	1	
	Yes	26 (8.2)	12 (3.8)	38 (11.9)	1.315 (.631- 2.74)	.465
Antiseizure	No	216 (67.7)	81 (25.4)	297 (93.1)	1	
	Yes	18 (5.6)	4 (1.3)	22 (6.9)	.593 (.195- 1.804)	.357
Antiplatelates	No	195 (61.1)	70 (21.9)	265 (83.1)	1	
	Yes	39 (12.2)	15 (4.7)	54 (16.9)	1.071 (.556- 2.063)	.836
Analgesic agents	No	168 (52.7)	61 (19.1)	229 (71.8)	1	
	Yes	66 (20.7)	24 (7.5)	90 (28.2)	1.001 (.577- 1.738)	.996
Gastrointestinal medicines	No	158 (49.5)	47 (14.7)	205 (64.3)	1	
	Yes	76 (23.8)	38 (11.9)	114 (35.7)	1.681 (1.012- 2.792)	.045
Number of medications	1-3 drugs	95 (29.8)	26 (8.2)	121 (37.9)	1	
	4-6 drugs	117 (36.7)	38 (11.9)	155 (48.6)	1.187 (.673- 2.093)	.554
	≥7 drugs	22 (6.9)	21 (6.6)	43 (13.5)	3.488 (1.666- 7.301)	.001
Medication error found	No	157 (49.2)	44 (13.8)	201 (63)	1	
	Yes	77 (24.1)	41 (12.9)	118 (37)	1.900 (1.146- 3.149)	.013

COR: crude odds ratio, CI: confidence interval, TB: Tuberculosis

5.10.4. Previous medication and medical condition of the patient related factors

History of medication use in the previous 3 months before the study period, being on medication during admission, previous medical condition of endocrine and metabolic disease and previous hospitalization in the previous 3 months were associated with occurrence of ADEs (**Table 14**).

Table 14: Univariate analysis of previous medication and medical condition of study participants at JMC, 2019

Variables		ADE occurrence		Total	COR (95% CI)	P value
		No; n (%)	Yes; n (%)	n (%)		
History of medication use in the past 3 months	No	125 (39.2)	28 (8.8)	153 (48)	1	
	Yes	109 (34.2)	57 (17.9)	166 (52)	2.335 (1.388- 3.927)	.001
On medication during admission	No	171 (53.6)	40 (12.5)	211 (66.1)	1	
	Yes	63 (19.7)	45 (14.1)	108 (33.9)	3.054 (1.825- 5.109)	.000
Antibiotics history	No	216 (67.7)	75 (23.5)	291 (91.2)	1	
	Yes	18 (5.6)	10 (3.1)	28 (8.8)	1.6 (.707- 3.62)	.259
Antivirals history	No	214 (67.1)	77 (24.1)	291 (91.2)	1	
	Yes	20 (6.3)	8 (2.5)	28 (8.8)	1.112 (.47- 2.628)	.809
Antidiabetic history	No	221 (69.3)	77 (24.1)	298 (93.4)	1	
	Yes	13 (4.1)	8 (2.5)	21 (6.6)	1.766 (.705- 4.424)	.225
Cardiovascular medicines history	No	182 (57.1)	58 (18.2)	240 (75.2)	1	
	yes	52 (16.3)	27 (8.5)	79 (24.8)	1.629 (.939- 2.827)	.082
Previous medical condition of circulatory system	No	173 (54.2)	58 (18.2)	231 (72.4)	1	
	Yes	61 (19.1)	27 (8.5)	88 (27.6)	1.320 (.768- 2.27)	.315
Previous medical condition of endocrine and metabolic disease	No	220 (69)	74 (23.2)	294 (92.2)	1	
	Yes	14 (4.4)	11 (3.4)	25 (7.8)	2.336 (1.016- 5.37)	.046
Previous medical condition of infectious disease	No	203 (63.6)	68 (21.3)	271 (85)	1	
	Yes	31 (9.7)	17 (5.3)	48 (15)	1.637 (.853- 3.143)	.138
Previous hospitalization in the past 3 months	No	187 (58.6)	56 (17.6)	243 (76.2)	1	
	Yes	47 (14.7)	29 (9.1)	76 (23.8)	2.06 (1.188- 3.574)	.010

COR: crude odds ratio, CI: confidence interval

5.10.5. Predictors of ADEs

Anti TB agents, disease of circulatory system, disease of digestive system, being on medication during admission and LOS ≥15 days were independent predictors of occurrence of ADEs (**Table 15**).

Patients with digestive system disease were 2.8 times more likely to experience ADEs than patients without this disease condition (AOR= 2.838, 95%CI: 1.446- 5.571, P= 0.002). Patients with circulatory system disease were about 2.7 times more likely to experience ADEs than patients without circulatory system disease (AOR= 2.669, 95% CI: 1. 456- 4.889, p= 0.001) (**Table 15**).

Patients who stayed 15 to 21 days in hospital had 4 times more likely to experience ADEs when compared to patients who stayed ≤7 days (AOR= 3.928, 95%CI: 1.388- 11.121, P= 0.010). Patients who stayed ≥22 days in hospital had 4.4 times more likely to experience ADEs when compared to patients who stayed ≤7 days (AOR= 4.348, 95%CI: 1.543- 12.254, P= 0.005) (**Table 15**).

Patients receiving anti TB agents were 2.5 times more likely to experience ADEs than patients who were not on anti TB agents (AOR= 2.523, 95%CI: 1.064- 5.982, P=0.036). Patients who were on medication at the time of admission were 3 times more likely to experience ADEs than who were not on medication during admission (AOR= 3.09, 95%CI= 1.766- 5.406, P= 0.000) (**Table 15**).

Table 15: Multivariate analysis, ADEs with different characteristics of study participants at JMC, 2019

Predictors		ADE occurrence		Total		P value
		No; n (%)	Yes; n (%)	n (%)	AOR (95% CI)	
Anti TB agents	No	210 (65.8)	66 (20.7)	276 (86.5)	1	
	Yes	24 (7.5)	19 (6)	43 (13.5)	2.523 (1.064- 5.982)	.036
Circulatory system disease	No	121 (37.9)	29 (9.1)	150 (47)	1	
	Yes	113 (35.4)	56 (17.6)	169 (53)	2.669 (1.456- 4.889)	.001
Digestive system disease	No	199 (62.4)	57 (17.9)	256 (80.3)	1	
	Yes	35 (11)	28 (8.8)	63 (19.7)	2.838 (1.446- 5.571)	.002

On medication during admission	No	171 (53.6)	40 (12.5)	211 (66.1)	1	
	Yes	63 (19.7)	45 (14.1)	108 (33.9)	3.09 (1.766- 5.406)	.000
LOS	1- 7 days	48 (15)	6 (1.9)	54 (16.9)	1	
	15-21 days	43 (13.5)	24 (7.5)	67 (21)	3.928 (1.388- 11.121)	.010
	≥ 22 days	50 (15.7)	32 (10)	82 (25.7)	4.348 (1.543- 12.254)	.005
	Constant				.033	.000

AOR: Adjusted odds ratio, CI: confidence interval, LOS: Length of hospital stay

Model performance:

The model containing all predictors was statistically significant ($\chi 2 = 59.816$, df= 5, $p < .000$), Hosmer and Lemeshow Test p = 0.816, indicating that the model was able to distinguish between patients who experienced ADEs and who didn't.

The pseudo r^2 (measure of effect): The model as a whole explained between 17.1% (Cox and Snell R square) and 24.9% (Nagelkerke R squared) of the variance in ADEs.

Accuracy of the model: The accuracy of the model in predicting ADE was assessed by evaluating the sensitivity and specificity. Sensitivity (true positive) is defined as the proportion of patients with an ADE who were correctly identified by the model. Specificity (true negative) is the proportion of patients without ADE who were recognized by the model.

Sensitivity of the model = 41.2%

Specificity of the model = 91.9%.

Positive predictive value: The percentage of cases that the model classified as having the ADE that is actually observed in this group is 64.81%, indicating that of the patients predicted to have ADE our model accurately picked 64.81 percent of them.

Negative predictive value: The percentage of cases predicted by the model not to have ADE that is actually observed not to have the ADE is 81.13%.

Discrimination of model: Discrimination of the model was assessed using area under receiver operating characteristics (AUROC) curve, which assess the ability of the model to predict ADE. AUROC indicates how well the model distinguishes patients who do not experience ADE from those with ADE. The AUROC value signifies the probability that a patient with an ADE had a higher predicted probability than a patient without ADE.

AUROC = 75.2% (95%CI: 68.9%- 81.5%) (**Figure 13**).

Area Under the Curve

Test Result Variables: Predicted probability

Area	Std. Error	P value	95% CI	
			Lower	Upper
.752	.032	.000	.689	.815

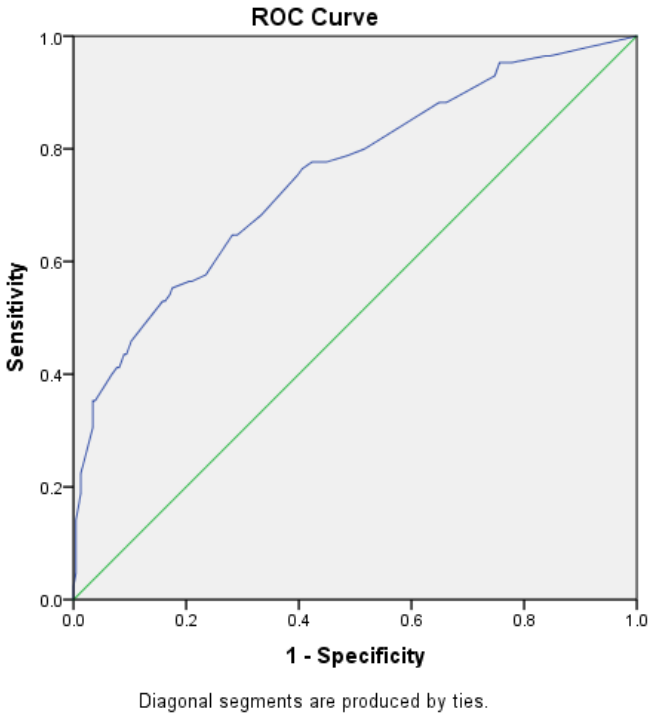


Figure 13: ADE predictor's model ROC curve, 2019.

5.11. Factors associated with potential ADEs

In univariate analysis, factors associated with potential ADEs were analgesics, antiviral agents, anticoagulants, anti-seizures, cardiovascular medicines, number of medications, CCI ≥ 6 and previous hospitalization in the past 3 months (**Table 16**).

Table 16: Univariate analysis, potential ADEs with different characteristics of study participants at JMC, 2019

Variables		Potential ADEs occurrence		Total	COR (95% CI)	P value
		No; n (%)	Yes; n (%)	n (%)		
Residence	Rural	163 (51.1%)	62 (19.4%)	225 (70.5%)	1	
	Urban	62 (19.4%)	32 (10%)	94 (29.5%)	1.357 (.809- 2.276)	.247
Previous hospitalization	No	179 (56.1%)	64 (20.1%)	243 (76.2%)	1	
	Yes	46 (14.4%)	30 (9.4%)	76 (23.8%)	1.824 (1.062- 3.134)	.030
Alcohol consumption	No	159 (49.8%)	73 (22.9%)	232 (72.7%)	1	
	Yes	66 (20.7%)	21 (6.6%)	87 (27.3%)	.693 (.394- 1.218)	.202
Number of medications	1-3 drugs	99 (31%)	22 (6.9%)	121 (37.9%)	1	
	4-6 drugs	108 (33.9%)	47 (14.7%)	155 (48.6%)	1.958 (1.102- 3.48)	.022
	≥7 drugs	18 (5.6%)	25 (7.8%)	43 (13.5%)	6.25 (2.917- 13.39)	.000
CCI	0-5	196 (61.4%)	69 (21.6%)	265 (83.1%)	1	
	≥ 6	29 (9.1%)	25 (7.8%)	54 (16.9%)	2.449 (1.342- 4.467)	.004
LOS	1- 7 days	37 (11.6%)	17 (5.3%)	54 (16.9%)	1	.124
	8-14 days	88 (27.6%)	28 (8.8%)	116 (36.4%)	.693 (.339- 1.415)	.314
	15-21 days	50 (15.7%)	17 (5.3%)	67(21.0%)	.740 (.334- 1.639)	.458
	≥ 22 days	50 (15.7%)	32 (10.0%)	82 (25.7%)	1.393 (.674- 2.878)	.371
Genitourinary system disease	No	155 (48.6%)	73 (22.9%)	228 (71.5%)	1	
	Yes	70 (21.9%)	21 (6.6%)	91 (28.5%)	.637 (.363- 1.117)	.115
Blood & immune disease	No	159 (49.8%)	74 (23.2%)	233 (73%)	1	
	Yes	66 (20.7%)	20 (6.3%)	86 (27.0%)	.651 (.368- 1.153)	.141

Endocrine & metabolic disease	No	181 (56.7%)	69 (21.6%)	250 (78.4%)	1	
	Yes	44 (13.8%)	25 (7.8%)	69 (21.6%)	1.49 (.848- 2.619)	.165
Digestive system disease	No	185 (58%)	71 (22.3%)	256 (80.3%)	1	
	Yes	40 (12.5%)	23 (7.2%)	63 (19.7%)	1.498 (.838- 2.679)	.173
Antivirals	No	215 (67.4%)	83 (26%)	298 (93.4%)	1	
	Yes	10 (3.1%)	11 (3.4%)	21 (6.6%)	2.849 (1.167- 6.96)	.022
Anticoagulants	No	197 (61.8%)	70 (21.9%)	267 (83.7%)	1	
	Yes	28 (8.8%)	24 (7.5%)	52 (16.3%)	2.412 (1.311- 4.438)	.005
Anti TB agents	No	200 (62.7%)	76 (23.8%)	276 (86.5%)	1	
	Yes	25 (7.8%)	18 (5.6%)	43 (13.5%)	1.895 (.978- 3.669)	.058
GI medicines	No	152 (47.6%)	53 (16.6%)	205 (64.3%)	1	
	Yes	73 (22.9%)	41 (12.9%)	114 (35.7%)	1.611 (.983- 2.64)	.059
Cardiovascular medicines	No	108 (33.9%)	57 (17.9%)	165 (51.7%)	1	
	Yes	117 (36.7%)	37 (11.6%)	154 (48.3%)	.599 (.367- .978)	.040
Anti-seizures	No	221 (69.3%)	76 (23.8%)	297 (93.1%)	1	
	Yes	4 (1.3%)	18 (5.6%)	22 (6.9%)	13.086 (4.29- 39.88)	.000
Analgesics	No	169 (53%)	60 (18.8%)	229 (71.8%)	1	
	Yes	56 (17.6%)	34 (10.7%)	90 (28.2%)	1.71 (1.019- 2.871)	.042
History of medication use in the past 3 months	No	114 (35.7%)	39 (12.2%)	153 (48%)	1	
	Yes	111 (34.8%)	55 (17.2%)	166 (52%)	1.448 (.890- 2.356)	.136

COR: crude odds ratio, CI: confidence interval

5.12. Predictors of potential ADEs

Number of medications, antiviral agents, anti-seizures, anti TB agents and anticoagulants were independent predictors of potential ADEs (**Table 17**).

Patients who received ≥7 medications were 3.9 times more likely to experience potential ADEs when compared to patients who received ≤ 3 drugs (AOR= 3.943, 95% CI: 1.688- 9.210, P= 0.002). Patients who were receiving antiviral agents were 3.2 times more likely to experience potential ADEs than patients who were not receiving antiviral agents (AOR= 3.222, 95%CI:

1.156- 8.981, P= 0.025). Patients who were on anticoagulants were about 3 times more likely to develop potential ADEs than who were not on anticoagulants (AOR= 2.989, 95%CI: 1.488- 6.004, P= 0.002). Patients receiving anti TB were 2.2 times more likely to develop potential ADEs than who were not on anti TB (AOR= 2.197, 95%CI: 1.039- 4.644, P= 0.039). Patients who were on anti-seizures were 21.7 times more likely to develop potential ADEs than who were not on anti-seizures (AOR= 21.667, 95%CI: 6.675- 70.330, P= 0.000) (**Table 17**).

Table 17: Multivariate analysis, potential ADEs with different characteristics of study participants at JMC, 2019

Predictors		Potential ADE occurrence		Total		P value
		No; n (%)	Yes; n (%)	n (%)	AOR (95% CI)	
Anti TB agents	No	200 (62.7%)	76 (23.8%)	276 (86.5%)	1	
	Yes	25 (7.8%)	18 (5.6%)	43 (13.5%)	2.197 (1.039- 4.644)	.039
Anticoagulants	No	197 (61.8%)	70 (21.9%)	267 (83.7%)	1	
	Yes	28 (8.8%)	24 (7.5%)	52 (16.3%)	2.989 (1.488- 6.004)	.002
Antiviral agents	No	215 (67.4%)	83 (26%)	298 (93.4%)	1	
	Yes	10 (3.1%)	11 (3.4%)	21 (6.6%)	3.222 (1.156- 8.981)	.025
Anti-seizures	No	221 (69.3%)	76 (23.8%)	297 (93.1%)	1	
	Yes	4 (1.3%)	18 (5.6%)	22 (6.9%)	21.67 (6.675- 70.33)	.000
Number of medications	1- 3 drugs	99 (31%)	22 (6.9%)	121 (37.9%)	1	
	≥ 7 drugs	18 (5.6%)	25 (7.8%)	43 (13.5%)	3.943 (1.688- 9.21)	.002
	Constant				.148	.000

AOR: Adjusted odds ratio, CI: confidence interval, TB: Tuberculosis

Model performance:

The model containing all predictors was statistically significant, $\chi 2 = 69.037$, df= 7 $p < .000$, Hosmer and Lemeshow Test $p = 0.617$, indicating that the model was able to distinguish between patients with potential ADEs and without potential ADEs.

The model as a whole explained between 19.5% (Cox and Snell R square) and 27.7% (Nagelkerke R squared) of the variance in potential ADEs.

Sensitivity (true positives) = 36.2%

Specificity (true negatives) = 95.1%.

Positive predictive value: The percentage of cases that the model classified as having the potential ADE that is actually observed in this group is 75.56%, indicating that of the patients predicted to have potential ADE our model accurately picked 75.56 percent of them.

Negative predictive value: The percentage of cases predicted by the model not to have potential ADE that is actually observed not to have the potential ADE is 78.1%.

AUROC = 76.5% (95%CI: 70.8%- 82.3%) (**Figure 14**).

Area Under the Curve

Test Result Variables: Predicted probability

Area	Std. Error	P value	95% CI	
			Lower	Upper
.765	.029	.000	.708	.823

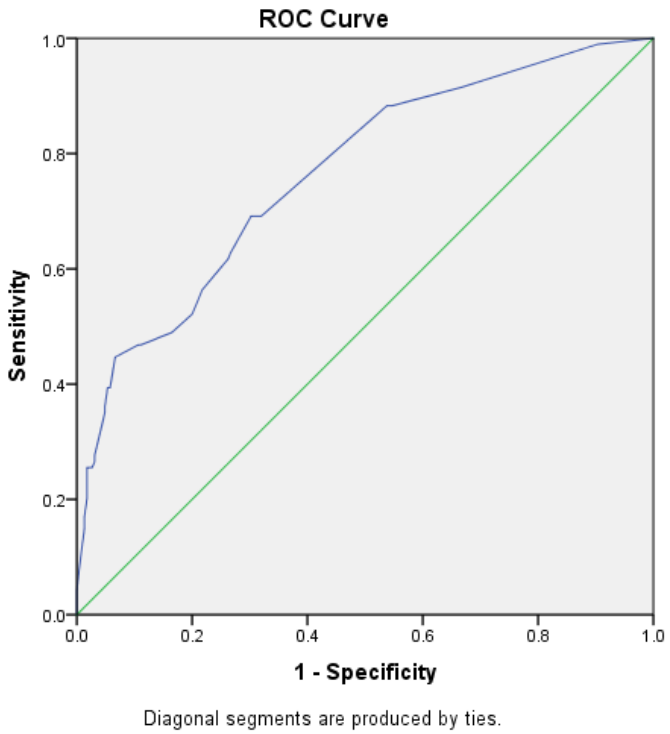


Figure 14: Potential ADE predictor's model ROC curve, 2019.

6. DISCUSSION

The incidence of ADEs in this study was found to be 36.36 (95% CI 30.05- 43.61) per 100 admissions (crude rate), 20.47 (95% CI 16.91- 24.55) per 1000 person days and 8.32 (95% CI 6.87- 9.97) per 100 medication orders, which is consistent with the range of results from prospective studies in hospitalized patients which used a similar method as the present study (23, 34, 72, 84, 85). However, the figure in our study is higher than which were observed in a prospective study by Aljadhey *et al* in Riyadh, Saudi Arabia (19), 6.1 (95% CI 5.4 to 6.9) per 100 admissions and 7.9 (95% CI 6.9 to 8.9) per 1000 patient-days. This might be the mean ± SD length of hospital stay of the patients was higher (17.8 ± 14.5 days Vs 8.1±10.2 days) in our study and Aljadhey *et al* included surgical unit. Our finding is lower than the study finding of 49.5% in Uganda (86). This might be differences in disease pattern and seasonal variation.

The causal relationship between the drug and the event as measured by the Naranjo algorithm were 26.72% definite, 60.34% probable and 12.93% possible ADEs which is comparable with prospective study by Sevilla *et al* in Spain (87) assessed by Naranjo algorithm. However, less number of definite and probable events was reported; definite (2%), probable (27%), in prospective study by Kiguba *et al* (34) in Uganda using similar causality measurement. This might be less number of laboratory data on assessment of ADEs was used as reported by authors.

In our study the most frequent system organ affected by ADEs are in line with other recent studies (34, 48, 88-90) i.e., ADEs affecting gastrointestinal system (30.17%), endocrine and metabolic (21.55%), hematologic (12.93%) and cardiovascular system (19.83%) were among the most frequently observed events whereas other organ systems including genitourinary system (3.45), respiratory system (0.86), central nervous system (2.59), neuromuscular and skeletal system (4.31), dermatologic (3.45) and immune system (0.86) were less frequently involved.

Regarding the medication classes accountable for ADEs, antibiotics, anti TB, diuretics, steroids, anticoagulants, cardiovascular drugs and analgesics have been most frequently reported in the literature (19, 34, 48, 51, 90). In our study, diuretics (26.47%), antibiotics (16.67%), anti TB (14.71%), cardiovascular drugs (10.78%) and anticoagulants (8.82%) were the most commonly implicated drug classes leading to occurrence of ADEs.

The severity of ADEs was assessed by modified Hartwig severity assessment scale and categorized as mild (37.07%), moderate (52.59%) and severe (10.34%) ADEs. The most of ADEs detected were moderate severity. With slight difference, Geer *et al* (48) found 41.52% mild, 48.83% moderate and 9.64% severe events while Sriram *et al* (91) reported 34.1% mild, 61.4% moderate and 4.5% severe events using similar assessment scale. Most of ADEs (37.93%) belonging to level 3 on the Hartwig's severity scale required that treatment with the suspected drug be held, discontinued, or otherwise changed and/or an antidote or other treatment was required and no increase in length of stay. Severe ADEs affected hematologic, endocrine and metabolic, dermatologic and gastrointestinal system.

Preventability of ADEs was assessed by modified Schumock and Thornton's preventability criteria. Most (62.07%) of ADEs was preventable (26.72% definitely preventable and 35.35% probably preventable) and 37.93% were non-preventable ADEs. Comparable to this, Sundaran et al (92) in India used similar criteria and reported 66.7% Preventable (definite 29.4% and probable 37.3%) and 33.3% not preventable events, Kiguba, *et al* (34) in Uganda found 54% preventable (definite 2% and probable 52%) and not preventable 45% events, Geer et al (48) in India found 81.58% preventable (definite 13.15% and probable 68.42%) and 18.42% not preventable events, Jayanthi et al (89) in India found 56% probably preventable and 44% not preventable events, Giardina et al (88) in Italy found 75.8% preventable (69.4% probable and 6.4% definite) and 24.2% not preventable events. In contrary to our study, Benkirane *et al* (42) in Morocco reported 70% of ADEs were non preventable. The discrepancy might be the authors didn't use prevention probability scores rather used the definition ADRs are non-preventable.

The incidence of potential ADEs were 29.47 (95% CI 23.8- 36.06) per 100 admissions (crude rate), 16.59 (95% CI 13.55- 20.3) per 1000 person days and 6.74 (95% CI 5.45- 8.25) per 100 medication orders. This is comparable with study by Aljadhey *et al* (19) in Riyadh, Saudi Arabia, which reported 16.9 (95% CI 15.7 to 18.3) Incidence per 100 admissions, 21.8 (95% CI 20.2 to 23.5) Crude rate per 1000 patient-days.

Multivariate analysis indicated that length of hospital stay, use of anti TB agents, disease of circulatory system, disease of digestive system and being on medication during admission independently predicted the occurrence of ADEs in this study. Discrimination ability of the model was assessed using AUROC, which indicates how well the model distinguishes patients

who do not experience ADE from those with ADE. The value of AUROC was 75.2% (95%CI: 68.9%- 81.5%).

The patients' length of hospital stay of 15 to 21 days (AOR= 3.928, 95%CI: 1.388- 11.121, P= 0.010) and greater than or equal to 22 days (AOR= 4.348, 95%CI: 1.543- 12.254, P= 0.005) independently strongly associated with occurrence of ADEs which is in line with another studies (29, 90, 93, 94). Tangiisuran *et al* (80) reported length of hospital stay more than or equal to 12 days were significantly associated with ADE occurrences (OR 2.3, 95%CI 1.35-3.83).

Among identified risk factors for ADEs, disease related factors were described in previous study (7). In our study, the medical condition of the patient was categorized according to ICD 10. Disease of circulatory system (AOR= 2.669, 95% CI: 1. 456- 4.889, p= 0.001) and disease of digestive system (AOR= 2.838, 95%CI: 1.446- 5.571, P= 0.002) were found to have significant association with occurrence of ADEs. This correlates with previous study by Urbina and colleagues (95) reported circulatory system (OR 1.892 95%CI: 1.400–2.557) and digestive system (OR 1.393 95%CI: 1.042–1.863) were associated with risk of adverse drug events. Other related findings were also reported (94). If liver (one of digestive system) functions less optimally; hence drugs are not readily metabolized and excreted. This leads to many drugs staying much longer than they do, the net result would be the prolongation of pharmacodynamic effects and occurrence of ADEs (96).

Anti TB agents were associated with occurrence of ADEs in this study (AOR= 2.523, 95%CI: 1.064- 5.982, P=0.036). Marra *et al* (97) reported anti TB agents independently associated with ADEs. The use of multi-drug regimens and over prolonged periods in TB treatment might be the reason (98).

Being on Medication during admission were found to have an association with occurrence of ADEs (AOR= 3.09, 95%CI= 1.766- 5.406, P= 0.000). Nguyen *et al* (99) reported treatment initiated before admission (OR 5.64 95%CI: 2.38- 13.36) and best possible medication history available (OR 0.50, 95%CI: 0.37- 0.67) has an association with occurrence of ADEs. Also Tangiisuran *et al* (80) articulated that the median number of medications taken by patients on admission was significantly higher in the ADR group compared with the non-ADR group (p=0.000).

The well-studied risk factor that have been reported in several previous reports (28, 29, 34, 90, 99), number of drugs prescribed for the patient showed an association in univariate analysis but eliminated in multivariate analysis because of its association with other factors and considered as confounder.

Multivariate analysis indicated that number of medications, antiviral agents, anti-seizures, anti TB agents and anticoagulants were independent predictors of potential ADEs. Discrimination ability of the model was assessed using AUROC, which is 76.5% (95%CI: 70.8%- 82.3%); thus the model demonstrated fair performance.

Patients who received greater than or equal to 7 medications had higher odds of experiencing potential ADEs among the study participants (AOR= 3.943 95% CI: 1.688- 9.210, P= 0.002). In line with this, Diaz and colleagues (24) reported an increased number of prescribed medications were significantly associated with all adverse events. Using multiple drugs concurrently, ADEs results from alterations of the pharmacokinetics parameters (96).

Anticoagulants were independently associated with occurrence of potential ADEs (AOR= 2.989 95%CI: 1.488- 6.004, P= 0.002). Anticoagulant requires a careful balance between thrombotic and hemorrhagic risks and is easily influenced by a multitude of factors, such as patient age, co-morbidities, concomitant medications, and for warfarin especially, diet and pharmacogenetics. Potential ADEs associated with anticoagulants vary depending on the types of anticoagulant agents, dosing strategies, prophylactic versus therapeutic indications, durations of therapy, and patient populations (3). In addition, anticoagulants have a narrow therapeutic window, and interactions affecting their pharmacokinetics or pharmacodynamics may result in potential ADEs (100)

Anti-seizures were significantly associated with occurrence of potential ADEs (AOR= 21.667 95%CI: 6.675- 70.330, P= 0.000). Anti-seizures may be combined with drugs used to treat intercurrent or associated conditions. When multiple drug therapy is used, there is a possibility of potential ADEs, which in patients with epilepsy are particularly common for a variety of reasons: (i) Anti-seizures are administered for prolonged periods, often for a lifetime, thereby increasing the probability of coprescription; (ii) most anti-seizures have a narrow therapeutic index, and even relatively modest alterations in their pharmacokinetics can result in loss of response or toxic effects; (iii) the most widely used anti-seizures (carbamazepine, valproic acid, phenytoin and

phenobarbital) have prominent effects on the activity of enzymes which metabolize the majority of existing medication; (iv) most of the old and new generation anti-seizures are substrates of the same enzymes (101).

Anti-TB were also found to have significant association with the occurrence of potential ADEs (AOR= 2.197 95%CI: 1.039- 4.644, P= 0.039). Three of the drugs that constitute the basic regimen (rifampin, isoniazid, and pyrazinamide) are potentially hepatotoxic. These drugs are metabolized in the liver and interact with other drugs, which occasionally increases the risk of hepatotoxicity. Genetic causes, advanced age, nutritional status, excessive doses of the drugs, use in combination with other hepatotoxic drugs, alcoholism, chronic viral hepatitis and HIV infection are predisposing factors for hepatotoxicity of anti TB agents (102).

Patients who were receiving antiviral agents were more likely to experience potential ADEs than patients who were not on this agents (AOR= 3.222 95%CI: 1.156- 8.981, P= 0.025). Mok *et al* (103) noted a significant number of potential ADEs of antiretroviral agents, leading to potentially severe ADEs. Anwikar and colleagues (104) observed highly significant association between use of zidovudine and anemia.

7. CONCLUSION

The incidence of ADEs identified in this study was consistent with published data. One in every four patients admitted in the ward experienced ADEs during their hospital stay. The most common (60.34%) were probable ADEs. Gastrointestinal system (30.17%), endocrine and metabolic (21.55%), hematologic (12.93%) and cardiovascular system (19.83%) were found the mostly affected organ system. The frequently implicated medication classes for development of ADEs were diuretics (26.47%), antibiotics (16.67%) and anti TB agents (14.71%).

Most (52.59%) of ADEs were moderate in severity. About two out of three cases were judged as either moderate or severe. Most (62.07%) of ADEs were definitely/probably preventable. That is about two third of the ADEs identified were deemed probably or definitely preventable. Anti TB agents, disease of circulatory and digestive system, being on medication during admission and length of hospital stay greater than or equal to 15 days were independent predictors of occurrence of ADEs.

The incidence of potential ADEs were 29.47 per 100 admissions, 16.59 per 1000 person days and 6.74 per 100 medication orders. The most common stage of medication use process at which potential ADEs occurred was at prescribing stage (67.02%). Number of medications, antiviral agents, anti-seizures, anti TB agents and anticoagulants were independent predictors of occurrence of potential ADEs.

8. RECOMMENDATION

Most of ADEs and all potential ADEs were deemed preventable. Preventing ADEs is a major priority for health care systems to improve patient safety. Based on our finding, we recommend the following:

For Healthcare professionals:

- Close monitoring and multidisciplinary communication on use of high-risk medications such as anti TB, antiviral agents, anti-seizures and anticoagulants.
- Improving prescribing safety and medication reconciliation for higher-risk medications may reduce the burden of ADEs
- Clinicians authorized for medication prescription and reconciliation should be vigilant for ADEs for higher-risk medications
- Report ADRs to pharmacovigilance center at JMC emphasizing on patients with disease of circulatory and digestive system, who stay more than two weeks in hospital, patients on greater than or equal to seven medications and patients on medication during admission, who are at risk of ADEs.

For JMC:

- Preventive measures should be taken emphasizing on patients with disease of circulatory and digestive system, who stay more than two weeks in hospital, patients on greater than or equal to seven medications and patients on medication during admission, who are at risk of ADEs.
- Developing anticoagulation standardized dosing algorithms and frequent monitoring of patients on anticoagulants.

For EFDA:

- EFDA pharmacovigilance center should consider these risk groups i.e. patients with disease of circulatory and digestive system, who stay more than two weeks in hospital, patients on greater than or equal to seven medications, patients on medication during admission, anti TB agents, antiviral agents, anti-seizures and anticoagulants to detect signals and request information from healthcare professionals.

For researchers:

- Use this study as baseline to perform further studies in the area of ADEs, especially its cost and impact in long study period.

REFERENCES

1. Federal Democratic Republic of Ethopia Ministry of Health Drug and Therapeutics Committee Training Course for health professionals. 2019.
2. Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (2014). Guideline for Adverse Drug Events Monitoring (Pharmacovigilance). https: //www.medbox.org/guideline-for-adverse-drug-events-monitoring-pharmacovigilance-ethiopia/download.pdf accessed 27 feb 2019.
3. Health UDo, Services H. National action plan for adverse drug event prevention. Washington (DC): Author. 2014;56.
4. Baneres J, Orrego C, Navarro L, Casas L, Banque M, Sunol R. [Epidemiology of the hospital adverse events in Catalonia, Spain: a first step for the patient safety improvement]. Med Clin. 2014;1:3-10.
5. Ducoffe AR, Baehr A, Pena JC, Rider BB, Yang S, Hu DJ. Adverse Drug Event Prevention: 2014 Action Plan Conference. Am J Med Qual. 2016;31(5):476-85.
6. Convertino I, Salvadori S, Pecori A, Galiulo MT, Ferraro S, Parrilli M, et al. Potential Direct Costs of Adverse Drug Events and Possible Cost Savings Achievable by their Prevention in Tuscany, Italy: A Model-Based Analysis. Drug Saf. 2018;1(10):018-0737.
7. Zhou L, Rupa AP. Categorization and association analysis of risk factors for adverse drug events. Eur J Clin Pharmacol. 2018;74(4):389-404.
8. WHO.10 facts on patient safety. https://www.who.int/features/factfiles/patient_safety/en/ Accessed 16 Jan 2019.
9. Amaral AC, McDonald A, Coburn NG, Xiong W, Shojania KG, Fowler RA, et al. Expanding the scope of Critical Care Rapid Response Teams: a feasible approach to identify adverse events. A prospective observational cohort. BMJ Qual Saf. 2015;24(12):764-8.
10. Hwang JI, Chin HJ, Chang YS. Characteristics associated with the occurrence of adverse events: a retrospective medical record review using the Global Trigger Tool in a fully digitalized tertiary teaching hospital in Korea. J Eval Clin Pract. 2014;20(1):27-35.
11. Kennerly DA, Kudyakov R, da Graca B, Saldana M, Compton J, Nicewander D, et al. Characterization of adverse events detected in a large health care delivery system using an enhanced global trigger tool over a five-year interval. Health Serv Res. 2014;49(5):1407-25.
12. Dalleur O, Beeler PE, Schnipper JL, Donze J. 30-Day Potentially Avoidable Readmissions Due to Adverse Drug Events. J Patient Saf. 2017;17(10)
13. Mekonnen AB, Alhawassi TM, McLachlan AJ, Brien JE. Adverse Drug Events and Medication Errors in African Hospitals: A Systematic Review. Drugs Real World Outcomes. 2018;5(1):1-24.
14. National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP). Defintion and types of medication errors. http://www.nccmerp.org/about-medication-errors. Accessed 09 Feb 2019.
15. Dedefo MG, Mitike AH, Angamo MT. Incidence and determinants of medication errors and adverse drug events among hospitalized children in West Ethiopia. BMC Pediatr. 2016;16(81):016-0619.
16. Jolivot PA, Hindlet P, Pichereau C, Fernandez C, Maury E, Guidet B, et al. A systematic review of adult admissions to ICUs related to adverse drug events. Crit Care. 2014;18(6):014-0643.

17. Laatikainen O, Miettunen J, Sneck S, Lehtiniemi H, Tenhunen O, Turpeinen M. The prevalence of medication-related adverse events in inpatients-a systematic review and meta-analysis. Eur J Clin Pharmacol. 2017;73(12):1539-49.
18. Lisha J, Annalakshmi V, Maria J, Padmini D. Adverse Drug Reactions in Critical Care Settings: A Systematic Review. Curr Drug Saf. 2017;12(3):147-61.
19. Aljadhey H, Mahmoud MA, Ahmed Y, Sultana R, Zouein S, Alshanawani S, et al. Incidence of adverse drug events in public and private hospitals in Riyadh, Saudi Arabia: the (ADESA) prospective cohort study. BMJ Open. 2016;6(7):2015-010831.
20. Ohta Y, Miki I, Kimura T, Abe M, Sakuma M, Koike K, et al. Epidemiology of Adverse Events and Medical Errors in the Care of Cardiology Patients. J Patient Saf. 2016;2(10):0000000000000291.
21. Sam AT, Lian Jessica LL, Parasuraman S. A retrospective study on the incidences of adverse drug events and analysis of the contributing trigger factors. J Basic Clin Pharm. 2015;6(2):64-8.
22. Giordani F, Rozenfeld S, Martins M. Adverse drug events identified by triggers at a teaching hospital in Brazil. BMC Pharmacol Toxicol. 2014;15(71):2050-6511.
23. Ohta Y, Sakuma M, Koike K, Bates DW, Morimoto T. Influence of adverse drug events on morbidity and mortality in intensive care units: the JADE study. Int J Qual Health Care. 2014;26(6):573-8.
24. Diaz Hernandez SH, Cruz-Gonzalez I. Incidence and Preventability of Medication Errors and ADEs in Ambulatory Care Older Patients. Consult Pharm. 2018;33(8):454-66.
25. Ayani N, Sakuma M, Morimoto T, Kikuchi T, Watanabe K, Narumoto J, et al. The epidemiology of adverse drug events and medication errors among psychiatric inpatients in Japan: the JADE study. BMC Psychiatry. 2016;16(303):016-1009.
26. Seynaeve S, Verbrugghe W, Claes B, Vandenplas D, Reyntiens D, Jorens PG. Adverse drug events in intensive care units: a cross-sectional study of prevalence and risk factors. Am J Crit Care. 2011;20(6).
27. Fujita S, Iida S, Nagai Y, Shimamori Y, Koyano K, Moriyama Y, et al. Estimation of the number of patient deaths recognized by a medical practitioner as caused by adverse events in hospitals in Japan: A cross-sectional study. Medicine. 2017;96(39):0000000000008128.
28. van den Bemt PM, Egberts AC, Lenderink AW, Verzijl JM, Simons KA, van der Pol WS, et al. Risk factors for the development of adverse drug events in hospitalized patients. Pharm World Sci. 2000;22(2):62-6.
29. Harkanen M, Kervinen M, Ahonen J, Voutilainen A, Turunen H, Vehvilainen-Julkunen K. Patient-specific risk factors of adverse drug events in adult inpatients - evidence detected using the Global Trigger Tool method. J Clin Nurs. 2015;24(3-4):582-91.
30. Evans RS, Lloyd JF, Stoddard GJ, Nebeker JR, Samore MH. Risk factors for adverse drug events: a 10-year analysis. Ann Pharmacother. 2005;39(7-8):1161-8.
31. Kongkaew C, Hann M, Mandal J, Williams SD, Metcalfe D, Noyce PR, et al. Risk factors for hospital admissions associated with adverse drug events. Pharmacotherapy. 2013;33(8):827-37.
32. Formica D, Sultana J, Cutroneo PM, Lucchesi S, Angelica R, Crisafulli S, et al. The economic burden of preventable adverse drug reactions: a systematic review of observational studies. Expert Opin Drug Saf. 2018;17(7):681-95.
33. Angamo MT, Chalmers L, Curtain CM, Bereznicki LR. Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries: A Review of Prevalence and Contributing Factors. Drug Saf. 2016;39(9):847-57.

34. Kiguba R, Karamagi C, Bird SM. Incidence, risk factors and risk prediction of hospital-acquired suspected adverse drug reactions: a prospective cohort of Ugandan inpatients. BMJ Open. 2017;7(1):e010568.
35. Berhe DF, Juhlin K, Star K, Beyene KG, Dheda M, Haaijer-Ruskamp FM, et al. Adverse drug reaction reports for cardiometabolic drugs from sub-Saharan Africa: a study in VigiBase. Trop Med Int Health. 2015;20(6):797-806.
36. Boeker EB, Ram K, Klopotowska JE, de Boer M, Creus MT, de Andrés AL, et al. An individual patient data meta-analysis on factors associated with adverse drug events in surgical and non-surgical inpatients. Br J Clin Pharmacol. 2015;79(4):548-57.
37. Spector WD, Limcangco R, Furukawa MF, Encinosa WE. The Marginal Costs of Adverse Drug Events Associated With Exposures to Anticoagulants and Hypoglycemic Agents During Hospitalization. Med Care. 2017;55(9):856-63.
38. Weiss AJ, Elixhauser A. Characteristics of Adverse Drug Events Originating During the Hospital Stay, 2011: Statistical Brief #164.
39. Hug BL, Keohane C, Seger DL, Yoon C, Bates DW. The costs of adverse drug events in community hospitals. Jt Comm J Qual Patient Saf. 2012;38(3):120-6.
40. Senst BL, Achusim LE, Genest RP, Cosentino LA, Ford CC, Little JA, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health Syst Pharm. 2001;58(12):1126-32.
41. Wolfe D, Yazdi F, Kanji S, Burry L, Beck A, Butler C, et al. Incidence, causes, and consequences of preventable adverse drug reactions occurring in inpatients: A systematic review of systematic reviews. PLoS One. 2018;13(10).
42. Benkirane RR, Abouqal R, Haimeur CC, SS SECEK, Azzouzi AA, Mdaghri Alaoui AA, et al. Incidence of adverse drug events and medication errors in intensive care units: a prospective multicenter study. J Patient Saf. 2009;5(1):16-22.
43. Feleke SA, Mulatu MA, Yesmaw YS. Medication administration error: magnitude and associated factors among nurses in Ethiopia. BMC nursing. 2015;14(1):53.
44. Bifftu BB, Dachew BA, Tiruneh BT, Beshah DT. Medication administration error reporting and associated factors among nurses working at the University of Gondar referral hospital, Northwest Ethiopia, 2015. BMC nursing. 2016;15(1):43.
45. Berhe DF, Taxis K, Haaijer-Ruskamp FM, Mulugeta A, Mengistu YT, Burgerhof JGM, et al. Impact of adverse drug events and treatment satisfaction on patient adherence with antihypertensive medication - a study in ambulatory patients. Br J Clin Pharmacol. 2017;83(9):2107-17.
46. Angamo MT, Curtain CM, Chalmers L, Yilma D, Bereznicki L. Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study. PLoS One. 2017;12(10).
47. Patel TK, Patel PB. Incidence of Adverse Drug Reactions in Indian Hospitals: A Systematic Review of Prospective Studies. Curr Drug Saf. 2016;11(2):128-36.
48. Geer MI, Koul PA, Tanki SA, Shah MY. Frequency, types, severity, preventability and costs of Adverse Drug Reactions at a tertiary care hospital. J Pharmacol Toxicol Methods. 2016;81:323-34.
49. Chan SL, Ang X, Sani LL, Ng HY, Winther MD, Liu JJ, et al. Prevalence and characteristics of adverse drug reactions at admission to hospital: a prospective observational study. British journal of clinical pharmacology. 2016;82(6):1636-46.
50. Ampadu HH, Hoekman J, de Bruin ML, Pal SN, Olsson S, Sartori D, et al. Adverse drug reaction reporting in Africa and a comparison of individual case safety report

characteristics between Africa and the rest of the world: analyses of spontaneous reports in VigiBase®. Drug safety. 2016;39(4):335-45.
51. Suh DC, Woodall BS, Shin SK, Hermes-De Santis ER. Clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother. 2000;34(12):1373-9.
52. Mouton JP, Njuguna C, Kramer N, Stewart A, Mehta U, Blockman M, et al. Adverse Drug Reactions Causing Admission to Medical Wards: A Cross-Sectional Survey at 4 Hospitals in South Africa. Medicine. 2016;95(19):0000000000003437.
53. Aderemi-Williams RI, Awodele O, Boyle CA. Adverse drug reactions amongst adult patients admitted in Lagos State University Teaching Hospital Lagos, Nigeria. Curr Drug Saf. 2015;10(2):136-44.
54. Benkirane R, Pariente A, Achour S, Ouammi L, Azzouzi A, Soulaymani R. Prevalence and preventability of adverse drug events in a teaching hospital: a cross-sectional study. 2009.
55. Mouton JP, Mehta U, Parrish AG, Wilson DP, Stewart A, Njuguna CW, et al. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. Br J Clin Pharmacol. 2015;80(4):818-26.
56. Jennane N, Madani N, Oulderrkhis R, Abidi K, Khoudri I, Belayachi J, et al. Incidence of medication errors in a Moroccan medical intensive care unit. Int Arch Med. 2011;4(32):1755-7682.
57. Ajemigbitse AA, Omole MK, Erhun WO. An assessment of the rate, types and severity of prescribing errors in a tertiary hospital in southwestern Nigeria. Afr J Med Med Sci. 2013;42(4):339-46.
58. Ajemigbitse AA, Omole MK, Osi-Ogbu OF, Erhun WO. A qualitative study of causes of prescribing errors among junior medical doctors in a Nigeria in-patient setting. Ann Afr Med. 2013;12(4):223-31.
59. Yousif MA, Nizar S, Elmustafa MO, Mustafa MI, Bella MM. Investigation of medication prescribing errors in Wad Medani, Gezira, Sudan. Int J Risk Saf Med. 2011;23(1):11-6.
60. al Tehewy M, Fahim H, Gad NI, El Gafary M, Rahman SA. Medication Administration Errors in a University Hospital. J Patient Saf. 2016;12(1):34-9.
61. Blignaut AJ, Coetzee SK, Klopper HC, Ellis SM. Medication administration errors and related deviations from safe practice: an observational study. J Clin Nurs. 2017;26(21-22):3610-23.
62. Sada O, Melkie A, Shibeshi W. Medication prescribing errors in the medical intensive care unit of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. BMC Res Notes. 2015;8(448):015-1435.
63. Agalu A, Ayele Y, Bedada W, Woldie M. Medication prescribing errors in the intensive care unit of Jimma University Specialized Hospital, Southwest Ethiopia. J Multidiscip Healthc. 2011;4:377-82.
64. Agalu A, Ayele Y, Bedada W, Woldie M. Medication administration errors in an intensive care unit in Ethiopia. Int Arch Med. 2012;5(1):1755-7682.
65. Chen YC, Fan JS, Chen MH, Hsu TF, Huang HH, Cheng KW, et al. Risk factors associated with adverse drug events among older adults in emergency department. Eur J Intern Med. 2014;25(1):49-55.
66. Murff HJ, Patel VL, Hripcsak G, Bates DW. Detecting adverse events for patient safety research: a review of current methodologies. J Biomed Inform. 2003;36(1-2):131-43.
67. Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E, et al. Identifying adverse drug events: development of a computer-based monitor and comparison with

chart review and stimulated voluntary report. J Am Med Inform Assoc. 1998;5(3):305-14.
68. Gonzalez-Gonzalez C, Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Strategies to improve adverse drug reaction reporting: a critical and systematic review. Drug Saf. 2013;36(5):317-28.
69. Field TS, Gurwitz JH, Harrold LR, Rothschild JM, Debellis K, Seger AC, et al. Strategies for detecting adverse drug events among older persons in the ambulatory setting. Journal of the American Medical Informatics Association. 2004;11(6):492-8.
70. Institute for Health Care Improvement. Trigger Tool for Measuring Adverse Drug Events. http://www.ihi.org/resources/Pages/Tools/TriggerToolforMeasuringAdverseDrugEvents.aspx. Accessed 16 Jan 2019.
71. Griffin FA, Resar RK. IHI global trigger tool for measuring adverse events. Institute for Healthcare Improvement Innovation Series White Paper. 2009.
72. Carnevali L, Krug B, Amant F, Van Pee D, Gerard V, de Bethune X, et al. Performance of the adverse drug event trigger tool and the global trigger tool for identifying adverse drug events: experience in a Belgian hospital. Ann Pharmacother. 2013;47(11):1414-9.
73. Wayne W. Daniel. BIOSTATISTICS A Foundation for Analysis in the Health Sciences tenth edition. 2013; 192.
74. Snyder RA, Fields W. A model for medication safety event detection. Int J Qual Health Care. 2010;22(3):179-86.
75. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care. 2004;13(4):306-14.
76. National Coordinating Council for Medication Error Reporting and Prevention. Taxonomy and Index for Categorizing Medication Errors. https://www.nccmerp.org/types-medication-errors Accessed 16 Jan 2019.
77. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992;27(6):538.
78. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
79. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. Qual Saf Health Care. 2003;12(3):194-200.
80. Tangiisuran B. Predicting adverse drug reactions in the hospitalised elderly [PhD Thesis]. Brighton: University of Sussex; 2009.
81. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49:2229-32.
82. Risha I. Patel, Robert D. Beckett. Evaluation of resources for analyzing drug interactions.J Med Libr Assoc. 2016; 104(4).
83. World Health organization. Glossary of terms related to patient and medication safety.https://www.who.int/patientsafety/highlights/COE_patient_and_medication_safety_gl.pdf. Accessed 8 april 2019.
84. Tribiño G, Maldonado C, Segura O, Díaz J. Costos directos y aspectos clínicos de las reacciones adversas a medicamentos en pacientes hospitalizados en el servicio de medicina interna de una institución de tercer nivel de Bogotá. Biomédica. 2006;26(1):31-41.

85. Grenouillet-Delacre M, Verdoux H, Moore N, Haramburu F, Miremont-Salame G, Etienne G, et al. Life-threatening adverse drug reactions at admission to medical intensive care: a prospective study in a teaching hospital. Intensive Care Med. 2007;33(12):2150-7.
86. Tumwikirize WA, Ogwal-Okeng JW, Vernby A, Anokbonggo WW, Gustafsson LL, Lundborg SC. Adverse drug reactions in patients admitted on internal medicine wards in a district and regional hospital in Uganda. Afr Health Sci. 2011;11(1):72-8.
87. Sevilla-Sanchez D, Molist-Brunet N, Amblas-Novellas J, Roura-Poch P, Espaulella-Panicot J, Codina-Jane C. Adverse drug events in patients with advanced chronic conditions who have a prognosis of limited life expectancy at hospital admission. Eur J Clin Pharmacol. 2017;73(1):79-89.
88. Giardina C, Cutroneo PM, Mocciaro E, Russo GT, Mandraffino G, Basile G, et al. Adverse Drug Reactions in Hospitalized Patients: Results of the FORWARD (Facilitation of Reporting in Hospital Ward) Study. Front Pharmacol. 2018;9(350).
89. CR J. A study to analyze the pattern, causality, severity, predictability and preventability of adverse drug reactions among patients attending department of obstetrics and gynecology at a tertiary care hospital. Journal of ICT Research & Applications. 2019;9(2).
90. Haile DB, Ayen WY, Tiwari P. Prevalence and assessment of factors contributing to adverse drug reactions in wards of a tertiary care hospital, India. Ethiop J Health Sci. 2013;23(1):39-48.
91. Sriram S, Senthilvel N, Divya et al.Detection, Monitoring and Assessment of Adverse Drug Reactions at a Private Corporate Hospital. International Journal of Science and Research. 2013; 2319-7064.
92. Sundaran S, Udayan A, Hareendranath K, Eliyas B, Ganesan et al. Study on the Classification, Causality, Preventability and Severity of Adverse Drug Reaction Using Spontaneous Reporting System in Hospitalized Patients. Pharmacy. 2018; 6, 108.
93. Amelung S, Meid AD, Nafe M, Thalheimer M, Hoppe-Tichy T, Haefeli WE, et al. Association of preventable adverse drug events with inpatients' length of stay-A propensity-matched cohort study. Int J Clin Pract. 2017;71(10):5.
94. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, et al. Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes.PLoS ONE. 2009;4(2)
95. Urbina O, Ferrandez O, Grau S, Luque S, Mojal S, Marin-Casino M, et al. Design of a score to identify hospitalized patients at risk of drug-related problems. Pharmacoepidemiol Drug Saf. 2014;23(9):923-32.
96. Malangu N. Introductory Chapter: Linkages between Pharmacokinetics and Adverse Effects of Drugs. Pharmacokinetics and Adverse Effects of Drugs-Mechanisms and Risks Factors: IntechOpen; 2018.
97. Marra F, Marra C, Bruchet N, Richardson K, Moadebi S, Elwood R, et al. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. The International Journal of Tuberculosis and Lung Disease. 2007;11(8):868-75.
98. Michael O, Sogaolu O, Fehintola F, Ige O, Falade C. Adverse events to first line anti-tuberculosis drugs in patients co-infected with HIV and tuberculosis. Annals of Ibadan postgraduate medicine. 2016;14(1):21-9.
99. Nguyen TL, Leguelinel-Blache G, Kinowski JM, Roux-Marson C, Rougier M, Spence J, et al. Improving medication safety: Development and impact of a multivariate model-based strategy to target high-risk patients. PLoS One. 2017;12(2).

100. Harder S, Thurmann P. Clinically important drug interactions with anticoagulants. An update. Clin Pharmacokin 1996; 30: 416–44.
101. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. British journal of clinical pharmacology. 2006;61(3):246-55.
102. Arbex MA, Varella MdCL, Siqueira HRd, Mello FAFd. Antituberculosis drugs: drug interactions, adverse effects, and use in special situations - part 1: first-line drugs. J bras pneumol. 2010;36:626-40.
103. Mok S, Minson Q. Drug-related problems in hospitalized patients with HIVinfection. Am J Health Syst Pharm. 2008; 65(1):55–59.
104. Anwikar SR, Bandekar MS, Smrati B, Pazare AP, Tatke PA, Kshirsagar NA. HAART induced adverse drug reactions: a retrospective analysis at a tertiary referral health care center in India. Int J Risk Saf Med. 2011; 23:163–169.

ANNEXES

Annex I. Data collection tools

Participant Consent Information Form

Title of the study: Adverse Drug Events and Contributing factors among Hospitalized Patients at Jimma Medical Center, South West Ethiopia: A Prospective Observational Study

Investigator: Tamiru Sahilu (B. Pharm.)

Advisor: Mrs. Mestawet Getachew (B.Pharm, Msc in clinical pharmacy)

Name of study area: medical ward, Jimma Medical Center, South West Ethiopia

Purpose of the Study: To assess adverse drug events and contributing factors among hospitalized patients at Jimma Medical Center. To understand how much patients are exposed to injury as a result of adverse drug events.

Study procedures: If you agree to take part in this study, you will be interviewed on various issues such as socio-economic and demographic characteristics, and practices of your medication.

Risks and costs: There are no expected risks associated with this study. There is no cost to participate in this research study and also there is no any incentive to be given for participation.

Benefits: Useful in order to develop better preventive strategies in the future and may also have the potential of being extrapolated to other hospitals

Right to refuse or withdraw: Your participation is voluntary. You may withdraw from this study at any time without any penalty.

Confidentiality: All information about the patients will be kept confidential. The data are stored without pateint's name and only used for the purpose of this study.

Agreement: Patients are expected to be fully voluntary to participate in the study

Contact: If you have any question or inconveniency, kindly you can contact principal investigator (Tamiru Sahilu) through the following addresses: Telephone: +251912459204, Email: tamepfsa@gmail.com

<u>የ ጥና ቱ ተሳ ታፊ ሚ ጃ ቅጽ</u>

የ ጥና ቱ ር ዕ ስ፡ በ ጅማ ዩ ኒ ቨ ር ሲ ቲ የ ሕክ ምና ሜ ዲ ከል ሆ ስ ፒ ታል ውስ ጥ ተ ኝ ተ ው ታ ካ ሚ ዎች ላ ይ የ ሚ ድ ሀ ኒ ቶች የ ጎ ን ዮ ሽ ጉ ዳ ቶ ችና አ ስ ተ ዋ ጽ ኦ ያ ላ ቸ ው ምክ ን ያ ቶ ች

ጥና ቱን የ ሚ ያ ካ ሄ ድ፡ አ ቶ ታ ምሩ ሳ ህ ሉ (B.Pharm.)

አ ማ ካ ሪ : ወ/ሮ ማ ክ ታ ወ ት ጌ ታ ቸ ው(B.Pharm., MSc. ክ ሊ ኒ ካ ል ፋ ር ማ ሲ)

የ ጥና ት ቦ ታ ስ ም የ ውስ ጥ ደ ዌ ህ ክ ምና ክ ፍ ል, ጅ ማ ዩ ኒ ቨ ር ሲ ቲ የ ሕ ክ ምና ሜ ዲ ከ ል, ደ ቡ ብ ምዕ ራ ብ ኢ ት ዮ ጵ ያ

የ ጥና ቱ ዓ ላ ማ በ ተ ለ ያ ዩ ምክ ን ያ ት ሚ ድ ሀ ኒ ቶች የ ሚ ያ ዞ ር ሱ ትን የ ጎ ን ሽ ጉ ዳ ቶ ችና አ ስ ተ ዋ ጽ ኦ ያ ላ ቸ ው ምክ ን ያ ቶ ች ማ ጥና ት ነ ው ፡ ይህ ጥና ት አ ስ ፈ ላ ጊ ነ ቱ በ ዋ ና ነ ት እ ን ደ ዚ ህ አ ይ ነ ት ች ግ ሮ ች ወ ደ ፊ ት ማ ላ ከ ል የ ሚ ያ ስ ች ል ስ ል ት ለ ሚ ቀ የ ስ የ ሚ ከ ቅ ም ነ ው ፡

የ ጥና ቱ ቅ ደ ም ተ ከ ተ ል-በ ዚ ህ ጥና ት ለ ማ ሳ ተ ፍ ከ ተ ስ ማ ሙ እ ን ደ ማ ህ በ ራ ዊ, ኢ ኮ ኖ ሚ ያ ዊ እ ና የ ሜ ድ ኃ ኒ ት ዎ ል ምዶ ች በ ተ ለ ያ የ ጉ ዳ ይ ላ ይ ቃ ለ-ማ ኪ ይ ቅ ይ ደ ረ ግ ል ዎ ታ ል፡ ፡

ስ ጋ ቶ ች እ ና ወ ጪ ዎ ች: ከ ዚ ህ ጥና ት ጋ ር የ ተ ዛ ማ ጁ አ ደ ጋ ዎ ች የ ሉ ም ፡ በ ዚ ህ የ ምር ምር ጥና ት ውስ ጥ ለ ማ ሳ ተ ፍ ምን ም ወ ጪ የ ለ ው ም እ ን ዲ ሁ ም ለ ማ ሳ ተ ፍ ምን ም ማ በ ረ ታ ቻ አ ይ ሰ ጥ ም ፡

ጥ ቅ ማ ጥ ቅ ሞ ች: ለ ወ ደ ፊ ቱ የ ተ ሻ ለ የ ማ ከ ላ ከ ያ ዘ ዴ ዎ ች ለ ማ ዳ በ ር ኢ ን ዲ ሁ ም ለ ሌ ሎ ች ሆ ስ ፒ ታ ሎ ች ት ን በ ያ ሊ ያ ደ ር ግ ይ ች ላ ል፡ ፡ በ ተ ጨ ማ ሪ ም ህ ማ ም ሞ በ አ ሳ ሳ ቢ ደ ረ ጃ ላ ይ የ ሚ ኝ ከ ሆ ነ የ ጡ ፍ ባ ለ ሞ ያ ለ ማ ጋ ገ ር ይ ጠ ቅ ም ዎ ታ ል፡ ፡

ለ ማ ከ ል ከ ል ወ ይ ም የ ሞ ት ው ጣ ባ ት: የ እ ር ስ ዎ ተ ሳ ት ፎ በ ፈ ቃ ደ ኝ ነ ት ነ ው ፡ በ ማ ን ኛ ው ም ጊ ዜ ያ ለ ም ን ም ቅ ጣ ት ከ ዚ ህ ጥና ት ሊ ያ ቋ ር ጡ ይ ች ላ ሉ፡ ፡

ሚ ስ ጢ ራ ዊ ነ ት፡ ስ ለ ታ ካ ሚ ዎች ሚ ጃ ሁ ሉ በ ሚ ስ ጥ ር ይ ያ ዛ ል፡ ፡ ሚ ጃ ው በ ኮ ድ የ ሚ ያ ዝ ሲ ሆ ን ለ ዚ ህ ጥና ት ጥ ቅ ም ብ ቻ የ ሚ ው ል ነ ው ፡

ስ ም ማ ቶ ች፡ የ እ ና ን ተ ተ ሳ ት ፎ በ ዚ ህ ምር ምር ላ ይ በ ማ ሉ ፍ ቃ ደ ኝ ነ ት ላ ይ የ ተ መ ሰ ረ ተ ነ ው ፡

አ ድ ራ ሻ : በ ጥና ቱ ላ ይ ያ ለ ዎ ትን ጥ ያ ቄ ለ አ ቶ ታ ምሩ ሳ ህ ለ በ ስ ል ክ ቁ ጥ ር 0912459204 ወ ይ ም Email: tamepfsa@gmail.com ማ ስ ተ ላ ለ ፍ እ ን ደ ሚ ች ሉ እ የ ገ ለ ጽ ኩ ስ ለ ት ብ ብ ር ዎ እ ና ማ ሳ ግ ና ለ ን፡ ፡

Odeeffannoo namoota qorannoo kana irratti hirmaataniif

Mataduree qoranichaa: Namoota hospitaala yuunibarsiitii Jimma ciisanii yaalaman irratti wantoota qorichootni miidhaa dabalataa akka fidan gummaacha godhan

Qorannoo kana kan gaggeessu: obbo Taammiruu Saahiluu (B. Pharm)

Mariisistuu: Aadde Mastaawat Getaachoo (B.Pharm., MSc.)

Iddoo qorannichaa: hospitaala yuunibarsiitii Jimma

Kaayyoo qorannichaa: Faayidaan qorannoo kanaa Namoota hospitaala yuunibarsiitii Jimma ciisanii yaalaman irratti wantoota qorichootni miidhaa dabalataa akka fidan gummaacha godhan fi rakkoowwan akkanaa fuulduratti haala itti ittisuun danda'amu mala dha'uu ta'a.

Faayidaa argattan ilaalchisee: Qorannoo kana irratti hirmaachuu keessaniif kallattiin faayidaa argattan yoo hinjiraanne illee, qorannichi dhibee kamiifiyyuu kan isin hin saaxille dha. Dabalataanis dhukkubni keessan sadarkaa hammaataa irra yoo jiraate, ogeessa fayyaa hospitaalichaa siniif dubbisuuf sin fayyada.

Haala hirmaannaa ilaalchisee: Qoranno kana keessatti hirmaannan keessan fedhii irratti kan hundaa'e ta'ee, yeroo barbaddan adeemsa qorannoo keessaa of fo'u ni dandeessu. Ragaaleen waa'ee keessan ibsan hundi icitiin kan qabamanii fi qaama biraatif hinkennaman. Gaaffii yookiin ilaalacha yoo qabaattan obbo Taammiruu Saahiluu lakkoofsa bilbilaa 0912459204 yookin Email: tamepfsa@gmail.com irratti qunnamuu dandeessu. Galatooma.

JIMMA UNIVERSITY

INSTITUTE OF HEALTH

SCHOOL OF PHARMACY

Participant written informed consent form

Dear research participant,

I am Tamiru Sahilu from school of pharmacy and Masters Student in clinical pharmacy. I am conducting a research on medication safety problems. The purpose of the study is to understand how much patients are exposed to injury as a result of adverse drug events. The results obtained from this study are useful in order to develop better preventive strategies in the future and may also have the potential of being extrapolated to other hospitals.

Your participation in the study is voluntary and that you can choose not to be included in the study or withdraw at any time. Your refusal not to participate will in no way affect your service at the hospital. All personal identifiers will be removed and no personal information will be forwarded to others. You may not personally derive any benefits directly from participating in the study and also there is no any risk or harm that this research will bring to you.

Your personal information will be maintained through use of unique codes and restricted access to the data set to the principal investigator and those working with him. I am very much grateful for your keen interest and honesty in sharing information. Whenever you have any questions or comments please contact Tamiru Sahilu: phone No: 0912459204. Email: tamepfsa@gmail.com

Date:_____ Signature of interviewer _____ Signature of respondent _____

በጅማ ዩኒቨርሲቲ የሕክምና ማዕከል ሆስፒታል ውስጥ ተኝተው ታካሚዎች ላይ የሚድሀኒቶች የጎንዮሽ ጉዳቶች ውጤቶችና አስተዋጽኦ ያላቸውምክንያቶች

አቶ ታምሩ ሳህሉ በፋርማሲ ት/ት ክፍል የማስተርስ ድግሪ የመመረቅያ ምርምሩን በዚህ ሆስፒታል ለህክምና በተኙ ታካሚዎች የሚድሀኒቶች የጎንዮሽ ጉዳቶች ውጤቶችና አስተዋጽኦ ያላቸው ምክንያቶች የሚያጠና ሲሆን የጥናቱ ዋና አላማ በተለያዩ ምክንያቶች መድሀኒቶች የሚያደርሱትን ጉዳት ውጤቶችና አስተዋጽኦ ያላቸውምክንያቶች ማጥናት ነው ፡ ይህ ጥናት አስፈላጊነቱ በዋናነት እንደዚህ አይነት ችግሮች ወደ ፊት ለማላከል የሚያስችል ስልት ለመቀየስ የሚጠቅምነው ፡

የእናንተ ተሳትፎ በዚህ ምርምር ላይ በፍቃደኝነት ላይ የተመሰረተ ሲሆን በማንኛውምሰዓት በምትፈልጉበት ግዜ ከምርምሩ ራሳችሁን ማግለል ትችላላችሁ፡ ፡ ስለእናንተ ማንነት የሚ ልጹ ሚጃዎች ጥናቱ በሚስጥር የሚይዝ ሲሆን ሚጃዎችንም ለሌላ ሶስተኛ ወገን አሳልፎ አይሰጥም ፡

በዚህ ምርምር ላይ በማሳተፍ በቀጥታ የሚያስገኝልዎት ጥቅምባይኖርምምርምሩ በርስዎ ላይ ምንምአይነት ጉዳት አያደርስም ፡ በጥናቱ ላይ ያለዎትን ጥያቄ ለአቶ ታምሩ ሳህሉ በስልክ ቁጥር 0912459204 ወይም Email: tamepfsa@gmail.com ማስተላለፍ እንደሚችሉ እየገለጽኩ ስለትብብርዎ እናመሰግናለን፡ ፡

ቀን _____

የጤያቂውፊርማ_____

የጥናቱተሳታፊ ፊርማ_____

Yuunibarsiitii Jimmaa

Institutii saayinsii fayyaa

Muummee faarmaasii

Namoota hospitaala yuunibarsiitii Jimma ciisanii yaalaman irratti wantoota qorichootni badii dabalataa akka fidan gummaacha godhan

Barataa digrii lammafaa kiliinikal Faarmaasi Taammiruu Saahiluu qorannoo eebbaa namoota hoospitaala kana ciisanii yaalaman irratti, wantoota qorichootni badii dabalataa akka irraan ga'an gummaacha godhan kan ilaalu dha. Faayidaan qorannoo kanaa rakkoowwan akkanaa fuulduratti haala itti ittisuun danda'amu mala dha'uu ta'a.

Qoranno kana keessatti hirmaannan keessan fedhii irratti kan hundaa'e ta'ee, yeroo barbaddan adeemsa qorannoo keessaa of fo'u ni dandeessu. Ragaaleen waa'ee keessan ibsan hundi icitiin kan qabamanii fi qaama biraatif hinkennaman.

Qorannoo kana irratti hirmaachuu keessaniif kallattiin faayidaa argattan yoo hinjiraanne illee, qorannichi dhibee kamiifiyyuu kan isin hin saxille dha. Ragaan dhuunfaa keessanii icitiin kan qabamu yoo ta'u gaaffii yookiin ilaalacha yoo qabaattan obbo Taammiruu Saahiluu lakkoofsa bilbilaa 0912459204 yookin Email: tamepfsa@gmail.com irratti qunnamuu dandeessu. Galatooma.

Guyyaa_____

Mallattoo gaafataa_____

Mallattoo qorannoo irratti hirmaatuu_____

Part I. Socio-demographic, diagnosis and drug therapy data collection form

S. No.	Variables	Response
1	Admission Unit:	
2	Card. No._____ Bed No.	
3	Date of admission	
4	Residence 1. Rural 2. Urban	
5	Age	
6	Sex:	1. M 2. F
7.	Traditional medicine use	1. yes 2. No
8	Alcohol use	1. Yes 2. No
9	Smoking status	1. Yes 2. No
10	Education	1. Uneducated 2. educated
11	Marital status	1. Married 2. Single 3. Widowed 4. Divorced
12	Occupation	1. Student 2. Gov't employee 3. Merchant 4. Self employed 5. Farmer 6. unemployed
13	Current working Diagnosis	

CCI

Medications ordered:-

Ser. No	Drug name	Dose, Route, Frequency,duration	Date started	Date stopped	Remarks

N.B. For PRN medication, please include the dose, time and date given

History of previous hospitalization with in 3months: yes No
Previous medical condition: yes No
If yes _____
History of medication use in the past 3months: Yes No
If yes write the medication_____
Number of medications the patient was receiving at admission_____

Final Diagnosis (Discharge summary):

For this patient, fill the following up on discharge:
1. Total number of medications the patient took:-
2. Outcome_____
3. Date of discharge: _____LOS_____

If there is any adverse drug event/incident identified at any time in this patient, please use the adverse drug event and /or medication error collection form.

Part II. ADVERSE DRUG EVENT DATA COLLECTION FORM

2. ADE found: Yes_____ NO_____

2.1. Describe the adverse drug event (ADE):

1.

2.

3.

Baseline lab result (if any)_____

Lab result at ADE (if any)_____

2.2. Date the event started:

2.3. Date the event stopped:

Time for appearance of ADE (day) after medication administered:

2.4. History of ADR:

2.5. Medication involved or suspected to involve ADE: (Name, dose, route, frequency, indication, date started)

1.

2.

3.

3. Treatment of ADE: YES_____NO_____

3.1. If yes, Please describe:

1.

2.

3.

3.2. Interventions: Please tick in the space for action taken in response to ADE

- Administration of antidote/reversal agent _____
- Medication dose changed _____
- Medication discontinued _____
- Required increased monitoring (Laboratory or vital sign)_____
- Transfer for higher level care_____
- Treatment_____
- Other intervention _____

  _____

4. Event Leading to ADE to occur in this patient:

If a medication error occurred, please use the medication error recording format

5. Does the patient have comorbid condition? Yes _____ No_____

If yes, 1. _____

2._____

3._____

Part III. ADE Patient Record Review Sheet

Total ADEs for this patient:

Naranjo Algorithm for causality Assessment

Question	Yes	No	Do Not Know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Definite ≥9, Probable 5-8, possible 1-4

Ser. No. ADE Found Harm Category* Description of ADE

*Harm Category

Category E: Temporary harm to the patient and required intervention

Category F: Temporary harm to the patient and required initial or prolonged hospitalization

Category G: Permanent patient harm

Category H: Intervention required sustaining life

Category I: Patient death

Modified Hartwig ADR Severity Assessment Scale	
Level 1	An ADR occurred but required no change in treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in LOS
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in LOS
Level 4	Any Level 3 ADR which increases length of stay by at least 1 day OR The ADR was the reason for the admission
Level 5	Any level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7a	The adverse reaction indirectly led to the death of the patient
Level 7b	The adverse reaction directly led to the death of the patient

Mild= level 1 and 2, Moderate= level 3 and 4, Severe= 5, 6, 7a and 7b.

Modified Schumock and Thornton's preventability criteria

Section A: Definitely preventable ADEs

1. Was the drug involved inappropriate for the patient's clinical condition?
2. Was the dose, route, or frequency of administration inappropriate for patient's age, weight or disease state?
3. Was there a history of allergy or previous reaction to the drug?
4. Was toxic serum drug concentration or lab monitoring test documented?
5. Was there a known treatment for ADEs?

Section B: Probably preventable ADEs

1. Was therapeutic drug monitoring or other necessary lab test not performed?
2. Was the drug interaction involved in ADEs?
3. Was poor compliance involved in ADE?
4. Were preventative measures not prescribed or administered to the patient?

Section C: Non-preventable ADEs

If all the above criteria not fulfilled

Part IV. MEDICATION ERROR COLLECTION FORM

1. Date of the event: _____(dd/mm/yr)

Time of the event: _____ (hh/mm 24 hr)

Admission Unit ME occurred:

2. Please describe the error, include description /sequence of events.

3. In which process did the error occurred:

_____ Prescribing _____ Dispensing (Including Filling) _____ Administration

_____ Monitoring _____ Transcribing

PRESCRIBING/ORDERING ERROR

___ Order written for wrong patient

____ Order written for wrong drug

_____drug not appropriate for indication

_____ Patient with allergy to drug

_____ drug-drug interaction

____ Order written for wrong dose/ dose not adjusted

____ Order written for wrong dosing schedule

____ Order written for wrong route

____other:

DISPENSING ERROR

_____ Wrong medication dispensed

_____Wrong dose dispensed

_____Expired drug dispensed

_____Wrong dosage form (route) dispensed

_____other:

MEDICATION ADMINISTRATION ERROR

___Medication omitted

___ Medication administered at wrong time

___Wrong medication administered

___Wrong dose administered

___Wrong route of administration

___Wrong dosage form of administration

___Medication given without physician order

___Medication given after physician order discontinued

MONITORING ERROR

____Necessary monitoring not ordered

____Necessary monitoring not performed

____Monitoring result not noted/ acted upon

____Other:

TRANSCRIBING ERROR

_____ Order transcribed for Wrong drug

_____ Order transcribed for Wrong dose

_____ Order transcribed for Wrong route

_____ Order transcribed for Wrong dosing schedule

_____ Order transcribed on Wrong patient

4. A). Did the error reach the patient: Yes (drug, dose, route, time administered) _____No (how error was intercepted) _____?

B). Describe the direct result on the patient (type of harm, additional patient monitoring required) if reaches the patient

C).Please Tick the appropriate error outcome category (select one)

No Error:

_____A. Potential error, circumstance / events have the potential to cause incident.

Error, No harm:

_____ B. Actual Error, did not reach the patient

_____ C. Actual Error, reached the patient but cause no harm

_____ D. additional monitoring required, cause no harm

Error, Harm:

_____ E. Treatment / intervention required - caused temporary harm

_____ F. Initial /prolonged hospitalization – caused temporary harm

_____G. Caused permanent harm

_____H. near death event - required intervention necessary to sustain life

Error, Death:

_____I. Death

6. Please complete the following for the medication involved.

Medication description	Medication Intended	Medication Error
1. Brand name:	_____	_____
2. Generic name (active ingredient):	_____	_____
3. Dose, Frequency, Duration, route:	_____	_____
4. Dosage form:	_____	_____
5. Strength/Concentration:	_____	_____

V. Questionnaire used to solicit information from the patient

1. Is there any medical problem in the past that you seek for treatment in the hospital/health center?

If yes, would you please share me?

_____

_____

_____

_____

2. A. Did you have taken any medications before you came to this Hospital? If so, what are those drugs?

_____

_____

B. While you were taking medications in the past, did you have any previous drug reactions/any allergic history to medications or food that you noted or you have been told by health professionals previously?

_____

_____

_____

3. While you are here;

A. Is there any new problem after you started to take your medications prescribed for your illness in the hospital after admission?

_____

_____

_____

_____

B. Is there any event that you noted in regards to your medications currently you are taking that reached you or intercepted before reaching you? If so, could you explain to me?

ከታካሚውሚጃ ለማከየቅ

1. ባለፉት ግዝያት በህመምምክንያት ሆስፒታል /የሕክምና ሜዕከል ህክምና ለሚድረግ ሄደውያውቃሉ? አዎ ከሆነ ,እባክዎን ያጋሩኝ?

_____

2. ወደዚህ ሆስፒታል ከመምጣትዎ በፊት ማንኛውንምዓይነት ሚድሃኒት ወስደዋል? ከሆነ ስ, እነዚህ ሚድሃኒቶች ምንድን ናቸው?

_____

3. ለህመምዎ የባህል ሚድሀኒት ወስደዋል? 1. አዎ 2. አልወሰድኩም
4. ቀደምባሉት ጊዜያት ሚድሃኒት እየወሰዱእያለ የሚድሃኒቶች የጎንዮሽ ጉዳት ወይም አለርጂ አጋጥሞት ያውቃል?

_____

5. አልኮል ይጠጣሉ? 1. አዎ 2. አልጠጣም
6. ሲጋራ ያጨሳሉ? 1. አዎ 2. አላጨስም
7. ትምህርት ተምረዋል? 1. አዎ 2. አልተማርኩም
8. አግብተዋል? 1. አግብቻለው? 2. አላገባሁም 3. አግብቶ የፈታ 4. በሞት ያጣ
9. የስራ ሁኔታ 1. ተማሪ 2. መንግሰት ሰራተኛ 3. ነጋዴ 4. የግል ስራ 5. አርሶ አደር 6. ስራ የለኝም
10. እዚሁእያሉ;

    ሀ. ሆስፒታል ከገቡበኋላ ለህመምዎ የታዘዘልዎትን ሚድሃኒት ሚውሰድ ከጀሚሩ በኋላ አዲስ ችግር አለ?

    _____

    ለ. በአሁኑ ጊዜ የሚድሃኒቶች የጎንዮሽ ጉዳት ወይምአለርጂ የደረሰብዎት አለ? ከሆነ ስ እባክዎን ያጋሩኝ?

    _____

Gaaffilee namoota qorannoo kana irratti hirmaatan gaafachuuf

1. kana dura dhukkubsattanii Hospitaala yookin buufata fayyaatti yaalamtanii beektuu?
_____
2. kana dura qorichi fudhachaa turtan ni jiraa?
_____
3. qoricha aadaa fudhattaniirtu? 1. Eeyyee 2. Lakkii
4. yommuu qoricha keessan fudhachaa turtan, miidhaan qorichi keessan sinirraan gahe yookiin alarjii sinirraan gahe ni jiraa?
_____

5. Alkoolii ni dhugduu? 1. Eeyyee 2. Lakkii
6. Sigaaraa ni xuuxxuu? 1. Eeyyee 2. Lakkii
7. Barumsa barattaniirtu? 1. Eeyyee 2. Lakkii
8. Haala gaa'ilaa: 1. Fuudhera 2. Hin fuune 3. Kan wal hiike 4. Du'aan kan dhabe
9. Hojiin idilee keessan maali? 1. Barataa 2. Hojjataa mootummaa 3. Daldalaa 4. Hojii dhuunfaa 5. Qotee bulaa 6. Hojii hin qabu
10. Erga as dhuftanii miidhaan qorichi keessan sinirraan gahe yookiin alarjii sinirraan gahe ni jiraa?
11. Qoricha fudhachaa jirtan waliin walqabatee dogongorri uumame ni jiraa?

Annex II. Trigger tool for measuring adverse drug events

T1. Diphenhydramine (Benadryl) - hypersensitivity reactions, drug rashes, extra pyramidal reactions

T2. Vitamin K- Warfarin toxicity or elevated International Normalized Ration (INR) levels

T3. Flumazenil- benzodiazepine overdose

T4. Anti-emetics (plasil) - Nausea and vomiting can be the result of drug toxicity or overdose

T5. Naloxone- narcotic overdose

T6. Anti-diarrheals- antibiotic-caused infections of Clostridium difficile.

T7. Sodium Polystyrene or insulin or calcium gluconate - treatment of hyperkalemia.

T8. Serum Glucose < 50mg/dl (hypoglycemia) - glucose (orally or IV), Dextrose 50% in water

T9. Clostridium difficile Positive Stool- Is likely, if a patient is on multiple antibiotics,

T10. Partial Thromboplastin Time (PTT) > 100 seconds- look for evidence of bleeding

T11. International Normalized Ration (INR) Level > 6- Look for evidence of bleeding

T12. White Blood Cell (WBC) Count < 3,000- will occur in response to drug administration.

T13. Platelet Count < 50,000- can be caused by certain medications, look for adverse events related to bleeding such as strokes, hematomas, and hemorrhage requiring blood transfusions.

T14. Digoxin immune fab (Digibind) - digoxin overdose

T15 Rising Serum Creatinine- check if the patient received nephrotoxic medications

T16 Over-sedation, Lethargy, fall, hypotension- look for sedative, analgesic, or muscle relaxant.

T17. Rash- look for evidence that the rash is related to drug administration.

T18. Abrupt Cessation of Medication- If "hold" medication orders appear, look for the reason.

T19. Transfer to a Higher Level of Care- in some cases an ADE is the cause

T20. Laxative or stool softeners (bisacodyl) - Look for drugs that has constipation effect

T21. Steroids (topical) - hypersensitivity reactions, drug rashes

T22. Steroids (injectable) - hypersensitivity reactions

T23. Protamine - heparin overdose

T24. Physostigmine - anticholineric overdose, alkaloids overdose

T25. Phentolamine - dopamine extravasation

T26. Glucagon - hypoglycemia, beta blocker overdose

T27. Phenytoin - seizures, arrhythmias

T28. Diazepam - drug induced seizures

T29. Epinephrine - hypersensitivity reactions

T30. Benzatropine/Trihexyphenidyl (artane) - extra pyramidal reactions

T31. Atropine – bradycardia

T32. Blood transfusion- Likely is related to a peri -operative adverse event.

T33. Cardiac or Pulmonary Arrest- check for medication-related issues

T34. Acute Dialysis- ADE might be drug-induced renal failure or reaction to the administration of a dye for radiological procedures.

T35. Decrease in Hg or Hematocrit of ≥25%- related to use of anticoagulants or aspirin or other

Annex III. Naranjo Algorithm for causality Assessment

Question	Yes	No	Do Not Know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Definite ≥9, Probable 5-8, possible 1-4, Doubtful≤ 0

Definite: The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.

Probable: The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

Possible: The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.

Doubtful: The reaction was likely related to factors other than a drug.

Questions	Yes	No	Do not Know
1. Are there previous conclusive reports on this reaction?	114	0	2
2. Did the adverse event appear after the suspected drug was administered?	107	1	8
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	49	1	66
4. Did the adverse reaction reappear when the drug was readministered?	62	1	53
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	24	69	23
6. Did the reaction appear when a placebo was given?	0	0	116
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	0	0	116
8. Was the reaction more severe when the dose was increased or less severe when dose decreased?	41	0	75
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	3	108	5
10. Was the adverse event confirmed by any objective evidence?	113	3	0

Instructions for Using the Naranjo Algorithm for causality Assessment

The response "Do not know" should be used sparingly and only when the quality of the data does not permit a "Yes" or "No" answer. "Do not know" can be applicable if the information is not available and also if the question is inapplicable to the case. When more than one drug is involved or suspected, the ADR algorithm is usually applied separately to each of the possible etiologic agents, and the drug with the highest score should be considered the causative agent. In addition, the potential of interaction should be evaluated.

Question 1. Are there previous conclusive reports on this reaction? The answer "Yes" (+1) applies if there have been two or more published reports in which the adverse reaction has been described in detail or if the adverse reaction is listed in a reliable source, such as a medical textbook, review article on the medication or on adverse drug reactions, or the product package insert. The response "No" applies when the adverse event has not been described previously or if only one report has been published, or if published reports were considered inconclusive or

unconvincing. The answer "Do not know" is applicable only when there is no information, because the agent has not been available for an adequate period of time or has not been previously evaluated for this adverse reaction. The scores given for "No" and "Do not know" are the same (0), so it is not critical to decide between these two answers.

Question 2. Did the adverse event appear after the suspected drug was administered? This question evaluates the temporal relationship between the reaction and administration of the medication. The answer "Yes" (+2) applies if there is definitive evidence that the adverse event occurred after the medication was started. "No" (-1) applies when the adverse event developed before the first dose of the drug. "Do not know" (0) applies if the information is not available or is unclear.

Question 3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered? This question evaluates the response to dechallenge or stopping the medication. The answer "Yes" (+1) applies if the adverse event diminishes or disappears at any time after stopping the medication, or if the reaction disappears upon administration of a specific pharmacologic antagonist (for example, an anticholinergic given for a cholinergic reaction to physostigmine). The answer "No" (0) applies if the adverse event does not improve or improves in response to a nonspecific therapy or an antidote to another medication or treatment of the underlying disease. The answer "Do not know" (0) applies if the medication was not stopped or the subsequent course was unknown, inconclusive or unclear.

Question 4. Did the adverse event reappear when the drug was readministered? This question evaluates the response to rechallenge or reexposure. An answer of "Yes" (+2) indicates that the medication was stopped, the adverse event resolved or improved, and there was an unequivocal reappearance or worsening of the reaction when the medicine was restarted in a similar dose and by the same route. The Naranjo scale also allows for a "Yes" if the causal association is well known and rechallenge cannot be done for clinical or ethical reasons. An answer of "No" (-1) only applies if rechallenge was done, but the adverse event did not reappear or worsen. The answer "Do not know" (0) applies if rechallenge was not done or information on rechallenge is not available or the reaction was ambiguous.

Question 5. Are there alternative causes that could on their own have caused the reaction? This question assesses alternative explanations for the adverse event. Because adverse events are

often nonspecific and can be manifestations of the disease being treated or an unrelated, concurrent disease or condition, other diagnoses need to be considered and excluded. The answer "No" (+2) applies if alternative causes have been excluded, based upon a systematic and complete evaluation, thus implicating the drug more strongly. A risk or susceptibility factor is not an alternative cause. The answer "Yes" (-1) applies when there is an alternative cause or explanation. "Do not know" (0) applies if the investigation of other causes is incomplete, inconclusive or was not done.

Question 6. Did the reaction reappear when a placebo was given? This question applies to clinical research studies in which a placebo was administered. The answer "Yes" (-1) applies if the medication was stopped and the adverse reaction resolved or improved conclusively, and there was an unequivocal reappearance of the adverse event after administration of placebo (single or double blind). The answer "No" (+1) applies if the reaction did not reappear or worsen after administration of placebo. "Do not know" (0) applies if placebo challenge was not done or the results were inconclusive.

Question 7. Was the drug detected in blood or other fluids in concentrations known to be toxic? This question applies specifically to dose dependent adverse reactions when blood, urine, tissue or other specimen concentrations of the medicine are available. The answer "Yes" (+1) applies if the concentration is in the accepted toxic or supratherapeutic range. "No" (0) applies if the concentration is below the toxic range. The answer "Do not know" (0) applies if drug levels are not available or are inconclusive.

Question 8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? This question evaluates the dose response relationship of medication and the adverse reaction. "Yes" (+1) applies if the adverse event was more severe or worsened when the dose of the medication was increased, or was less severe and improved when the dose was decreased. "No" (0) applies if there was no appreciable change in the severity of the adverse event with dose modification. "Do not know" (0) applies if the dose or regimen was not altered or the information was not available or inconclusive.

Question 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? This question is directed at past medical history of adverse reactions to the same or a structurally related drug. "Yes" (+1) applies when there is documentation of a previous similar

reaction to the specific drug or a related medication. "No" (0) applies when the patient does not have a previous exposure to the same medicine or when the patient did not develop the adverse reaction in a previous exposure to the same or related drugs. "Do not know" (0) applies when there is no information on previous reactions or the information is inconclusive.

Question 10. Was the adverse event confirmed by any objective evidence? The final question assesses the quality of the data on which the adverse event is assessed. "Yes" (+1) indicates that there is laboratory test documentation of the adverse event or that the event was directly observed by a qualified person (for example, a skin rash described in nursing or physician notes). The answer "No" (0) applies when neither laboratory tests nor direct clinical documentation can verify the reaction. "Do not know" (0) applies if there is no specific information available (no laboratory testing and no clinical description) or the information is inconclusive. The scores given for "No" and "Do not know" are the same (0), so it is not critical to decide between these two answers.

Annex IV. Modified Schumock and Thornton's preventability criteria

Section A: Definitely preventable ADEs

1. Was the drug involved inappropriate for the patient's clinical condition?

2. Was the dose, route, or frequency of administration inappropriate for patient's age, weight or disease state?

3. Was there a history of allergy or previous reaction to the drug?

4. Was toxic serum drug concentration or lab monitoring test documented?

5. Was there a known treatment for ADEs?

Section B: Probably preventable ADEs

1. Was therapeutic drug monitoring or other necessary lab test not performed?

2. Was the drug interaction involved in ADEs?

3. Was poor compliance involved in ADE?

4. Were preventative measures not prescribed or administered to the patient?

Section C: Non-preventable ADEs

If all the above criteria not fulfilled

The modified Schumock and Thornton's preventability criterion has three sections namely definitely preventable, probably preventable and non-preventable. Section A comprises of five questions while section B has four questions. All the answers are categorized as "Yes" or "No". ADRs were "definitely preventable" if answer was "yes" to one or more questions in section A. If answers were all negative then we proceeded to section B. ADRs were "probably preventable" if answer was "yes" to one or more questions in section B. If answers were all negative then we proceeded to section C. In Section C the ADRs were non-preventable.

Modified Schumock and Thornton's preventability criteria		Frequency	Percent
Section A	Was the drug involved inappropriate for the patient's clinical condition?	3	2.59
	Was the dose, route, or frequency of administration inappropriate for patient's age, weight or disease state?	27	23.28
	Was there a history of allergy or previous reaction to the drug?	1	0.86
Section B	Was therapeutic drug monitoring or other necessary lab test not performed?	5	4.31
	Was the drug interaction involved in ADEs?	3	2.59
	Were preventative measures not prescribed or administered to the patient?	33	28.45
Section C	If all the above criteria not fulfilled	44	37.93
	Total	116	100.00

Annex V. Modified Hartwig ADR Severity Assessment Scale

Modified Hartwig ADR Severity Assessment Scale	
Level 1	An ADR occurred but required no change in treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in LOS
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in LOS
Level 4	Any Level 3 ADR which increases length of stay by at least 1 day OR The ADR was the reason for the admission
Level 5	Any level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7a	The adverse reaction indirectly led to the death of the patient
Level 7b	The adverse reaction directly led to the death of the patient

Mild= level 1 and 2

Moderate= level 3 and 4

Severe= 5, 6, 7a and 7b.

Modified Hartwig ADR Severity Assessment Scale		Frequency	Percent
Level 1	An ADR occurred but required no change in treatment with the suspected drug	26	22.41
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in LOS	17	14.66
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in LOS	44	37.93
Level 4	Any Level 3 ADR which increases length of stay by at least 1 day OR The ADR was the reason for the admission	17	14.66
Level 6	The adverse reaction caused permanent harm to the patient	2	1.72
Level 7a	The adverse reaction indirectly led to the death of the patient	10	8.62
	Total	116	100