Current Therapeutic Research 93 (2020) 100611

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

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

Tamiru Sahilu, MSc[1,*], Mestawet Getachew, MSc[2], Tsegaye Melaku, MSc[2], Tadesse Sheleme, MSc[3]

[1] Department of Pharmacy, College of Health Science, Assosa University, Assosa, Ethiopia
[2] Department of Clinical Pharmacy, School of Pharmacy, Institute of Health, Jimma University, Jimma, Ethiopia
[3] Department of Pharmacy, College of Public Health and Medical Science, Mettu University, Metu Zuria, Ethiopia

ARTICLE INFO

Article history:
Received 4 September 2020
Accepted 18 October 2020

Key words:
Adverse drug event
Contributing factor
Incidence rate
Independent predictor
Patient safety
Prospective observational study

ABSTRACT

Background: Adverse drug events (ADEs) are common complications of clinical care resulting in significant morbidity, mortality, and high clinical expenditure. Population-level estimates of inpatient ADEs are limited in Ethiopia.
Objective: This study aimed to assess the incidence, contributing factors, severity, and preventability of ADEs among hospitalized adult patients at Jimma Medical Center, Ethiopia.
Methods: A prospective observational study design was conducted among hospitalized adult patients at tertiary hospital in Ethiopia. A structured data collection tool was prepared from relevant literatures for data collection. Data were analyzed using statistical software. Logistic regression was performed to identify factors contributing to ADE occurrence. P values < 0.05 were considered statistically significant.
Results: A total of 319 patients were included with follow-up period of 5667 person-days. About 50.5% were women. The mean (SD) age of patients was 43 (17.6) years. One hundred sixteen ADEs were identified with the incidence of 36.4 (95% CI, 30.1–43.6) per 100 admissions and 20.5 (95% CI, 16.9–24.6) per 1000 person-days. Antituberculosis agents (adjusted odds ratio [aOR] = 2.52; 95% CI, 1.06–5.98; $P = 0.036$), disease of the circulatory system (aOR = 2.67; 95% CI, 1.46–4.89; $P = 0.001$), disease of the digestive system (aOR = 2.84; 95% CI, 1.45–5.57; $P = 0.002$), being on medication during admission (aOR = 3.09; 95% CI, 1.77–5.41; $P < 0.001$), and hospital stay more than 2 weeks (aOR = 3.93; 95% CI, 1.39–11.12; $P = 0.010$) were independent predictors of ADE occurrence.
Conclusions: One in every 4 patients admitted to the hospital experienced ADEs during their hospital stay. Most ADEs were moderate in severity. About two-thirds of the ADEs identified were deemed probably or definitely preventable. Therefore, it is high time to reinforce large-scale efforts to redesign safer, higher quality health care systems to adequately tackle the problem.

Introduction

Adverse drug events (ADEs) are any untoward medical occurrence that may be present during treatment with medicine.[1,2] Institutes of Medicine defined ADEs as an "injury resulting from medical intervention related to a drug."[3] This includes medication errors, adverse drug reactions (ADRs), 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 health care systems and their prevention could be associated with a relevant cost-saving.[6] They are among the leading causes of morbidity and hospitalization in health facilities.[7] In a 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] The systematic review done by Jolivot et al[9] reported that the incidence of ADEs in adult inpatients ranged from 0.37%

* Address correspondence to: Tamiru Sahilu, MSc, Department of Pharmacy, College of Health Science, Assosa University, B40, 5220, Assosa, Ethiopia. Fax :+251 57 775 07 84.
E-mail address: tamepfsa@gmail.com (T. Sahilu).

https://doi.org/10.1016/j.curtheres.2020.100611

to 27.4%. The pooled prevalence estimate of inpatient ADEs ranged from 4.5% to 34.1%.[10,11]

A prospective cohort study done in 4 hospitals in Saudi Arabia showed the incidence of ADEs was 6.1 per 100 admissions.[12] The rate of ADEs ranges from 16.3 to 18.3 per 100 patients[13–15] and 7.9 to 30.6 per 1000 patient-days,[12,16] with potential for ADEs of 9.4 per 100 patient-years.[17] Evidence showed that ADEs caused life-threatening harm (1.4%), serious harm (28%),[18] temporary harm (96%), complications (4%),[19] and patient death of 1326 to 1433 per annum with a mortality rate of 8.81 to 9.52 cases per 100,000 patients.[20] Similarly, preventability ranges from 14.2% to 92.9%.[21–24] A systematic review done by Mekonnen et al[25] revealed that 43.5% of ADEs were deemed preventable in African hospitals.

Medication error is the most common ADE encountered on daily clinical services. National Coordinating Council for Medication Error Reporting and Prevention defines a 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."[26] They are a major health burden, contributing to 18.7% to 56% of all ADEs among hospitalized patients.[27]

A review of articles by Zhou et al[7] identified risk factors for ADEs and grouped them into 5 main categories: patient, disease, medication, health service, and genetics-related. Among these, medication and disease-related risk factors were most frequently reported in the scientific literature. Polypharmacy,[28] length of hospital stay,[29] comorbidity,[30] inappropriate use of drugs, cardiovascular agents, and anti-infection treatments[7] were identified as significantly associated risk factors for ADE. Older age, pill burden, and starting new high-risk drugs were found to have significant relationships with preventable ADEs.[31] A prospective, cross-sectional study conducted by Angamo et al[32] showed 10.3% of patients had ADR-related hospitalization. But, evidence related to incidence, severity, and preventability of ADEs in inpatients is lacking. 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. Information gained from this finding will be used for developing procedures, systems, and policies for improving patient safety internationally, nationally, regionally, and in individual organizations. Thus, reducing ADEs is expected to result in safer health care services, reduced health care costs, and improved health outcomes. The study aimed to assess the incidence of ADEs and determine the severity, preventability, and contributing factors for ADEs among hospitalized adult patients.

Methods

Study setting and period

The study was conducted among hospitalized patients at the medical ward of Jimma Medical Center (JMC). JMC is located 352 km from Addis Ababa, the capital city of Ethiopia. It is the only medical center in the southwest part of the country and has 800 active beds. It has a catchment population of more than 20 million. Hospital services are rendered by more than 2000 permanent staff (both technical and administrative). It serves more than 400,000 patients per year at emergency and outpatient departments and various inpatient wards. Among the wards, the medical ward has different units (ie, cardiac, neurology, pulmonology, general medicine, intensive care units, and renal care units). Because of financial constraints, the study was conducted in a single center. Conducting a multicenter study would produce more generalizable results as far as future implications or reproducibility of the work.

Study design and population

A prospective observational study was conducted among adult patients admitted to inpatient medical wards or units.

Participant eligibility and inclusion

All adult patients aged ≥18 years and admitted to the medical wards or units of JMC during the study period were screened for eligibility criteria. Patients taking at least 1 medication after admission and/or continuing at least 1 medication from a previous regimen who were willing to participate and who stayed >24 hours in the hospital were included in the study. Patients who had incomplete medical and medication records, unconscious patients, and patients admitted due to ADRs were excluded.

Sample size and sampling technique

The sample size was calculated based on the following assumption: $Z = 1.96$, the proportion of ADE occurrence $(P) = 0.525$ was taken from study done by Agalu et al,[33] and marginal error $(d) = 5\%$, then the sample size is equal to 384. The study population in the study setting; that is, the number of patients admitted to the medical wards of JMC from September 2018 to February 2019 (6 months) taken from admission/discharge registry of the hospital was 1171 patients. The calculated sample size using a correction formula was 289. Considering 10% for nonresponse, the final sample size was 319. A consecutive type of sampling technique was used to collect data from all patients who fulfilled the inclusion criteria.

Data collection instrument, procedures, and quality assurance

A semistructured questionnaire was designed by reviewing literature for important variables.[34–37] The questionnaire was translated into 2 local languages (Afaan Oromoo and Amharic) to solicit information from patients. Data were taken from patient medical charts, patient interviews, and direct observation. ADE Trigger Tool[36] and the medication module of the Institute for Healthcare Improvement Global Trigger Tool[38] for measuring ADEs was used to facilitate manual chart reviews and increase detection of ADEs. ADR causality was assessed by the Naranjo ADR probability scale[39] because it was developed and validated for the assessment of ADRs[40] and produced the most consistent results.[41] The Naranjo algorithm classifies the probability that an adverse event is related to drug therapy based on a list of weighted questions that examine factors such as the temporal association of drug administration and event occurrence, de-challenge/re-challenge, alternative causes for the event, adverse event confirmed by any objective evidence, and previous drug exposure. The World Health Organization-Uppsala Monitoring Center criteria[42] have been criticized for being subjective and imprecise.[43] The Karch and Lasagna[44] ambiguously manage factors that may be associated with adverse events.[40] None of the causality assessment tools have been universally accepted as the gold standard.[45]

ADEs are considered serious when they result in death, require hospital admission or prolongation of hospital stay, result in persistent or significant disability or incapacity, or are life-threatening.[46]

Training was given for data collectors on the data collection procedure and research objectives. Before exporting to SPSS statistical software (IBM-SPSS Inc, Armonk, NY), data were checked and cleared in EpiData (EpiData Association, Odense, Denmark) to exclude ambiguous, incomplete, and erroneous data.

Outcome measures and validating methods

Multimethod event detection methods[34] were employed to identify ADEs in the ward to maximize data yield. Data collectors did a chart review for all patients. Patients' medical records and documents such as the prescriber's progress chart, laboratory reports, physician orders, nursing progress chart, and data about drug exposure were assessed. During the chart review, trigger tools or clues[47] were used to facilitate ADE detection.[36,38] The list of laboratory reports reviewed were alanine aminotransferase, aspartate aminotransferase, blood urea, serum creatinine, complete blood count, blood glucose, serum electrolytes (eg, calcium, potassium, and sodium), coagulation profile (eg, prothrombin time, international normalized ratio), and electrocardiogram. For further information or clarification and confirmation of the cases, the patient was interviewed using the questionnaire and observed for medication related harm(s).

For evaluation, confirmation of cases, and exclusion of differential disease condition, a team of clinical pharmacists attended multidisciplinary ward rounds and discussed the suspected ADE cases for probability. All medical ward staff members were invited to inform the investigators of any incident that they noted during daily clinical services. The systematic approach recommended by Tangisuran et al,[48] including case identification, confirmation, and classification of incidents was applied to ensure the correct classification and to avoid inclusion of any doubtful cases that could overestimate the incidence of ADEs.

When suspected ADEs were identified, the investigators further evaluated its relationship with the medication using the Naranjo causality assessment algorithm.[39] Only those in the category of definite, probable, and possible were considered. The severity of the ADEs was categorized based on the modified Hartwig Severity Assessment Scale,[49] which classifies severity of ADEs as mild, moderate, or severe with 7 levels according to factors like requirements for change in treatment, length of hospital stay, caused permanent harm, and the ADE led to the death of the patient. Karch and Lasanga classify severity into minor, moderate, severe, and lethal.[50] The US Food and Drug Administration classifies an ADEs as serious when it results in death, is life-threatening, prolongs hospitalization, results in persistent or significant incapacity, or results in a congenital anomaly.[51] Because there is no preference of 1 assessment scale over the other, the authors decided to use the modified Hartwig Severity Assessment Scale, considering change in drug therapy of this scale as special factor. The preventability of ADEs was assessed using modified Schumock and Thornton's criteria.[52]

Data processing and analysis

All collected patient data were entered into EpiData version 4.4.1 and exported to SPSS version 24 for cleaning and analysis, respectively. Frequency and percentage of sociodemographic characteristics, clinical characteristics, diagnosis, medication ordered, previous medical condition, and medication history was calculated. Categorical variables were described as numbers and percentages, and continuous variables as mean (SD). Variables were tested for multicolinearity by collinearity diagnostics. Assumption of independence (adequacy of cells) was carried out by χ^2 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 multivariate logistic regression. Multivariate logistic regression was performed using a backward likelihood ratio to identify independent predictors of ADE occurrence. An odds ratio (OR) was used as a measure of the strength of association. A P value < 0.05 was considered to be statistically significant.

Outcome of the study was reported as ADE incidence per 100 admissions, per 1000 person-days, and per 100 medication orders; severity of ADEs; percentage of ADEs that were preventable or nonpreventable; the percentage of medication errors in stages of medication use (eg, ordering/prescribing, transcribing, dispensing, administering, or monitoring) responsible for ADE occurrence.

- ADEs incidence per 100 admissions: The total number of ADEs identified, divided by the total number of admissions; multiplied by 100.
- ADEs incidence per 1000 patient-days: The total number of ADEs identified, divided by the total number of patient-days multiplied by 1000.
- ADEs incidence per 100 medication orders: The total number of ADEs identified, divided by the sum of medications ordered multiplied by 100.

Ethical approval and consent to participate

Before commencement of the study, ethical approval was obtained from the Institutional Review Board of Jimma University (ref No.: IHRPGD/550/19). The hospital director and head of the department of internal medicine were informed about the purpose of the study to get permission and cooperation. Participants were informed about the purpose/nature of the study before the data collection and approved the invitation by written informed consent. The participants' information was kept confidential.

Results

Study population inclusion

During the 3-month study period, a total of 612 patients were assessed for eligibility at the medical ward of JMC. Of these, 319 patients were followed daily until discharge and included in the final analysis (Fig. 1).

Sociodemographic and clinical characteristics of the study participants

From a total of 319 participants, 161 (50.5%) were women. The mean (SD) age of the participants was 43 (17.6) years. About two-thirds of participants were married. Nearly one-third of study participants attended formal education. Most participants—225 (70.5%)—were from a rural area. About 27.3% of study participant consumed alcohol and 14 (4.4%) patients had used traditional medicine. Nearly one-fourth of study participants had a history of hospitalization during the 3 months before the study period. Eleven patients had a known history of ADRs. The mean (SD) and the total length of hospital stay of the patients was 17.8 (14.5) days and 5667 patient-days, respectively. Burden of comorbidities were determined by Charlson comorbidity index and the mean (SD) of Charlson comorbidity index was 2.8 (2.3). The mean (SD) number of medications prescribed to study participants was 4.4 (2) (Table 1).

Primary diagnosis of study participants

The primary diagnosis of the patients were categorized according to International Classification of Diseases tenth edition code. Most of the patients were diagnosed with diseases of the circulatory system (53%), infectious and parasitic diseases (34.5%), and diseases of the genitourinary system (28.5%) (Table 2).

Among the patients involved in the study, 171 (53.6%) had a previous medical condition. Diseases of the circulatory system (88

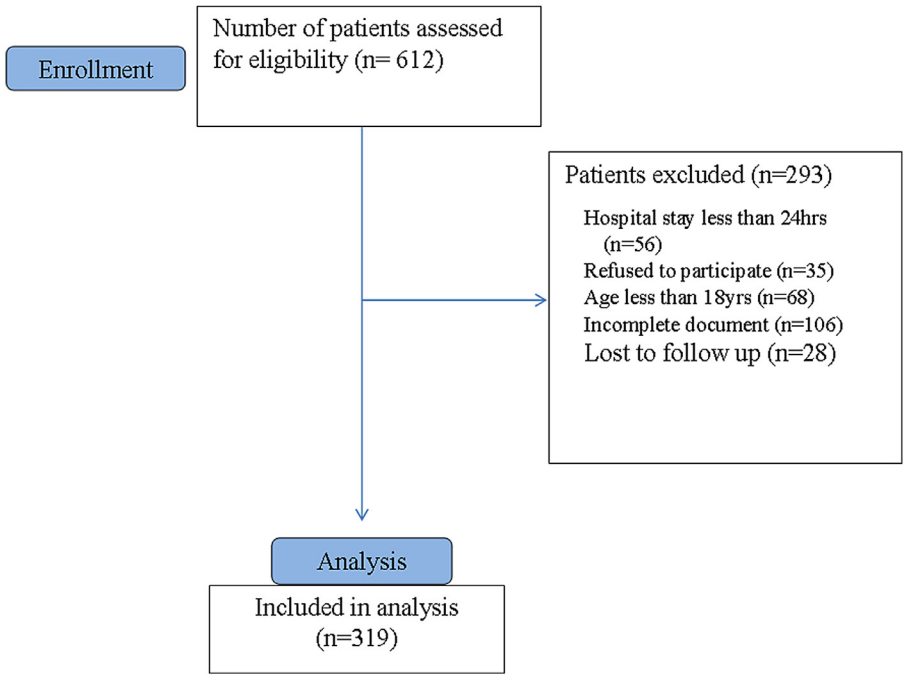

Fig. 1. Flow chart showing study participants inclusion.

Table 1
Sociodemographic and clinical characteristics of study participants.

Variable		Frequency	%
Sex	Male	158	49.5
	Female	161	50.5
Age, y	Average*	43 (17.6)	
	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	Married	213	66.8
status	Single	87	27.3
	Widowed	9	2.8
	Divorced	10	3.1
Educational	Uneducated	218	68.3
status	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 user		87	27.3
Cigarette smoker		26	8.2
Traditional medicine user		14	4.4
No. of medications	Average*	4.4 (2)	
	≤3	121	37.9
	4-6	155	48.6
	≥7	43	13.5
Had history of adverse drug reaction(s)		11	3.4
Had history of hospitalization in the previous 3 mo		76	23.8
Length of hospital stay*, d		17.8 (14.5)	
Charlson comorbidity index*		2.8 (2.3)	

* Values are presented as mean (SD).

[51.46%]); infectious and parasitic diseases (48 [28.07%]); and endocrine, nutritional, and metabolic diseases (25 [14.62%]) were the top-3 medical conditions of the patients (Table 3).

Table 2
The primary diagnosis of study participants.

ICD-10 code	Diagnosis	Frequency	%
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

ICD-10 = International Classification of Diseases, tenth edition.

Table 3
Previous medical condition of the study participants.

ICD-10 code	Diagnosis	Frequency (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

ICD-10 = International Classification of Diseases, tenth edition.

Table 4
Types of medication prescribed on admission for study participants.

Participant	Class of medication	Frequency	%
1	Antibiotics	162	50.8
2	Cardiovascular medicines	154	48.3
3	Gastrointestinal medicines	114	35.7
4	Analgesics	90	28.2
5	Vitamins and antianemic agents	78	24.5
6	Electrolytes	59	18.5
7	Antiplatelets	54	16.9
8	Antidyslipidemic agents	53	16.6
9	Anticoagulants	52	16.3
10	Antituberculosis agents	43	13.5
11	Steroids	38	11.9
12	Antidiabetic agents	27	8.5
13	Antiseizure agents	22	6.9
14	Antiviral agents	21	6.6
15	Antifungal agents	12	3.8
16	Antiasthma agents	11	3.4
17	Antithyroid agents	9	2.8
18	Antipsychotic agents	9	2.8
19	Antimalarials	6	1.9
20	Antihistamines	3	0.9

Table 5
Types of medication history reported by the study participants.

Participant	Class of medication	Frequency (n = 108]	%
1	Cardiovascular medicines	79	73.15
2	Antibiotics	28	25.93
3	Antivirals	28	25.93
4	Antituberculosis	11	10.19
5	Antiplatelet	11	10.19
6	Antidyslipidemic	10	9.26
7	Antiasthmatic	10	9.26
8	Gastrointestinal medicines	9	8.33
9	Steroids	7	6.48
10	Antimalarials	6	5.56
11	Anticoagulants	5	4.63
12	Antianemic agents	5	4.63
13	Antiseizure	5	4.63
14	Antipsychotic	4	3.70
15	Analgesics	3	2.78
16	Antithyroid agents	2	1.85

Admission medication(s)

A total of 1395 medications were prescribed for the study participants. Most of the patients received antibiotics (50.8%), cardiovascular medicines (48.3%), gastrointestinal medicines (35.7%), and analgesics (28.2%) (Table 4).

Medication history

Based on documented and available data, 166 (52%) patients had history of medication use during the 3 months before the study period. One hundred eight patients were taking medication during admission. Most patients were taking cardiovascular medicines (79 [73.15%]), antibiotics (28 [25.93%]), and antiviral agents (28 [25.93%]) (Table 5).

Incidence of ADEs

A total of 116 ADEs were identified during the 3 months of the study period. In total, these ADEs occurred on 85 (26.65%) patients. Twenty-two patients were found to have more than 1 ADE. 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 as a medication error. The stage of the medication use process at which medication error occurred was at prescribing stage (37 [88.1%]) and at monitoring stage (5 [11.9%]).

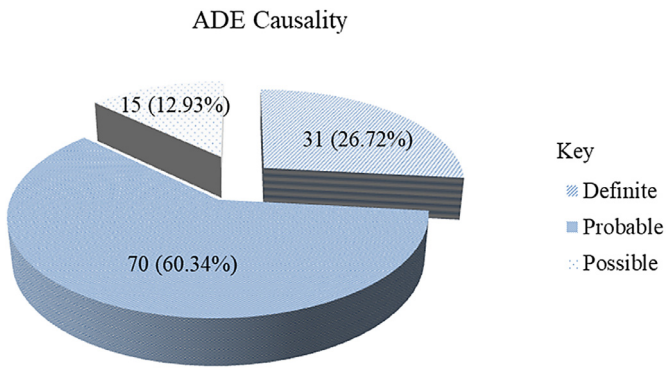

Fig. 2. Result of Naranjo causality assessment algorithm. ADE = adverse drug event.

The causal relationship between ADEs and an administered drug was established by the Naranjo algorithm. For each ADE, the algorithm was done and 31 (26.72%) ADEs occurrence were definite, 70 (60.34%) ADEs were probable, and 15 (12.93%) ADEs were possible causality (Fig. 2).

ADEs were categorized according to system organ affected by the ADE. The most common system organs influenced were the gastrointestinal system (35 [30.17%]), endocrine and metabolic (25 [21.55%]), hematology (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 6).

The common medication classes accountable for development of ADEs were diuretics (27 [26.47%]), antibiotics (17 [16.67%]), antituberculosis (15 [14.71%]), cardiovascular medicines (11 [10.78%]), anticoagulants (9 [8.82%]), and antidiabetes agents (6 [5.88%]). Furosemide (25 [24.5%); rifampicin, isoniazid, pyrazinamide, and ethambutol (9 [8.82%]); ceftriaxone (7 [6.86%]; enalapril (6 [5.88%]); cotrimoxazole (6 [5.88%]); and insulin (6 [5.88%]) were the most commonly involved medications (Table 7).

Severity and preventability of ADEs

According to modified Hartwig Severity Assessment Scale, 61 (52.59%) were moderate, 43 (37.07%) were mild, and 12 (10.34%) were severe (Table 8). Preventability of ADEs was assessed by modified Schumock and Thornton preventability criteria. Thirty-one (26.72%) were definitely preventable, 41 (35.35%) were probably preventable, and 44 (37.93%) were nonpreventable ADEs (Table 9).

Factors associated with occurrence of ADEs

Patient-related factors

The patient-related factors and ADEs occurrence association was analyzed and summarized in Table 10. In univariate analysis, patients with an age range of 51 to 65 years had an association with the occurrence of ADEs. Otherwise, there was no significant difference in patient-related characteristics (eg, sex, residence, educational status, alcohol consumption, smoking, and occupation) between patients who experienced ADEs and patients who did not.

Disease-related factors

The diagnosis of the patients was categorized according to International Classification of Diseases tenth edition code. Patients with the digestive system, circulatory system, and endocrine and metabolic disease had a significant association with the occurrence of ADEs. Also, the patients' length of hospital stay had a significant association with the occurrence of ADEs. Patients with digestive

Table 6
Incidence of adverse drug event (ADE) classification by organ system.

Organ system	Incidence*	ADE*	Medication involved (n)
Gastrointestinal	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 + ferrous sulfate (1)
		Dyspepsia 7 (6)	RHZE (4), salbutamol (1), RH (1), warfarin + UFH (1)
		Gastrointestinal ulcer 1 (0.9)	Aspirin (1)
		Hepatotoxicity† (5 serious ADEs) 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 gastrointestinal Bleeding 1 (0.9)	Furosemide (1)
Endocrine and metabolic	25 (21.55)	Hyperkalemia† (2 serious ADEs) 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† (3 serious ADEs) 11 (9.5)	Furosemide‡ (3), prednisolone (1), RHZE‡ (1), insulin‡ (5), gentamicin (1)
		Hyponatremia† (1 serious ADE) 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)
		Second-degree atrioventricular 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 + zidovudine (1)
		Pancytopenia† (1 serious ADE) 3 (2.6)	Phenobarbital (1), chlorpromazine (1), cotrimoxazole + zidovudine‡ (1)
		Thrombocytopenia† (1 serious ADE) 2 (1.7)	Amlodipine (1), UFH‡ (1)
		Bicytopenia (Platelets + red blood cell)† 1 (0.9)	Propylthiouracil (1)
		Bleeding† (2 serious ADEs) 4 (3.5)	Warfarin‡ (3), warfarin + UFH‡ (1)
Neuromuscular and skeletal	5 (4.31)	Peripheral neuropathy 5 (4.3)	Isoniazid (5)
Dermatologic	4 (3.45)	Skin rash 2 (1.7)	Cotrimoxazole (1), vancomycin (1)
		Toxic epidermal necrosis with Stevens-Johnson syndrome overlap† 1 (0.9)	Loratadine (1)
		Toxic epidermal necrosis† 1 (0.9)	Ivermectin (1)
Genitourinary	4 (3.45)	Increased blood urea nitrogen 1 (0.9)	Cotrimoxazole (1)
		Acute kidney injury† (1 serious ADE) 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	1 (0.86)	Dry cough† 1 (0.9)	Enalapril
Immune system	1 (0.86)	Allergy† 1 (0.9)	Cotrimoxazole
Total	116 (100)	116 (100%)	

RH = rifampicin, isoniazid; RHZE = rifampicin, isoniazid, pyrazinamide, ethambutol; UFH = unfractionated heparin.
* Values are presented as n (%).
† Serious ADEs (24 out of 116 [20.69%]).
‡ Medications involved in serious ADEs.

Table 7
Medications accountable for adverse drug events.

Medication class	Frequency (%)	Medications involved (n)
Diuretic	27 (26.47)	Furosemide (25), mannitol injection (1), spironolactone (1)
Antibiotic	17 (16.67)	Cotrimoxazole (6), gentamicin (1), metronidazole (1), ceftriaxone (7), vancomycin (2)
Antituberculosis	15 (14.71)	RH (1), RHZE (9), isoniazid (5)
Cardiovascular medicines	11 (10.78)	Metoprolol tartarate (1), digoxin (1), metoprolol succinate (2), enalapril (6), propranolol (1)
Anticoagulant	9 (8.82)	UFH (4), warfarin (5)
Antidiabetic	6 (5.88)	Insulin
Gastrointestinal medicines	3 (2.94)	Cimetidine (2), omeprazole (1)
Antiviral	2 (1.96)	Zidovudine (2)
Steroids	2 (1.96)	Prednisolone (1), dexamethasone (1)
Antipsychotic medicines	1 (0.98)	Chlorpromazine
Antihypertensive	1 (0.98)	Amlodipine
Antiasthmatic	1 (0.98)	Salbutamol
Antiseizure	1 (0.98)	Phenobarbital
Antithyroid agents	1 (0.98)	Propylthiouracil
Analgesics	1 (0.98)	Morphine
Antianemic agents	1 (0.98)	Ferrous sulphate
Antiplatelet	1 (0.98)	Aspirin
Antihistamine	1 (0.98)	Loratadine
Anthelmintic	1 (0.98)	Ivermectin
Total	102 (100)	

RH = rifampicin, isoniazid; RHZE = rifampicin, isoniazid, pyrazinamide, ethambutol; UFH = unfractionated heparin.

Table 8
Severity of adverse drug events based on modified Hartwig Adverse Drug Reaction (ADR) Severity Assessment Scale.

Level*	Description	Frequency	%
1	An ADR occurred but required no change in treatment with the suspected drug	26	22.41
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 length of hospital stay	17	14.66
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 length of hospital stay	44	37.93
4	Any Level 3 ADR which increases length of stay by at least 1 d OR the ADR was the reason for the admission	17	14.66
6	The adverse reaction caused permanent harm to the patient	2	1.72
7a	The adverse reaction indirectly led to the death of the patient	10	8.62
Total		116	100

* ADRs were considered mild (levels 1 and 2), moderate (levels 3 and 4), or severe (levels 6 and 7a).

system disease were 2.8 times more likely to experience ADEs than patients without this disease condition (adjusted OR [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 11).

Patients who stayed 15 to 21 days in hospital had 4 times more likely to experience ADEs compared with patients who stayed ≤7 days (aOR = 3.928; 95% CI, 1.388–11.121; $P = 0.010$). Patients who stayed ≥22 days in hospital were 4.4 times more likely to experience ADEs when compared with patients who stayed ≤7 days (aOR = 4.348; 95% CI, 1.543–12.254; $P = 0.005$) (Table 11).

Drug-related factors

Medications were categorized according to anatomic and therapeutic classification. Most patients received antibiotics (50.8%), cardiovascular medicines (48.3%), gastrointestinal medicines (35.7%), and analgesics (28.2%). Antituberculosis (anti-TB) agents, antidiabetes agents, gastrointestinal medicines, the number of medications the patient was receiving, and medication error were associated with the occurrence of ADEs. Patients receiving anti-TB agents were 2.5 times more likely to experience ADEs than patients who were not taking anti-TB agents (aOR = 2.523; 95% CI, 1.064–5.982; $P = 0.036$) (Table 12).

Previous medication and medical condition of the patient-related factors

Based on documented and available data, 166 (52%) patients had a history of medication use during the previous 3 months before the study period. One hundred eight (33.86%) patients were taking medication during admission. Most of the patients were on cardiovascular medicines (79 [24.8%]), antibiotics (28 [8.8%]), and antiviral agents (28 [8.8%]). History of medication use during the previous 3 months before the study period, being on medication during admission, previous medical condition of endocrine and metabolic disease, and hospitalization during the 3 months before the study period were associated with the occurrence of ADEs. Patients who were taking medication during admission were 3 times more likely to experience ADEs than those who were not taking medication during admission (aOR = 3.09; 95% CI, 1.766–5.406; $P < 0.0001$) (Table 13).

Discussion

Patient safety is a serious global public health concern. Using conservative estimates, the latest data show that patient harm is the fourteenth leading cause of morbidity and mortality across the world.[8] ADEs led to additional medical costs, prolonged hospitalization, morbidity, and ascribable disability worldwide.[53] They are largely preventable and occur mostly at the prescribing stage of the medication use process.[12]

In this study, the incidence of ADEs in hospitalized patients was evaluated and one-third were caused by medication error at prescribing and monitoring stage. The incidence in the present study is consistent with the range of results from prospective studies.[16,54–57] However, the figure in our study is higher than observed in a prospective study in Saudi Arabia: 6.1 per 100 admissions and 7.9 per 1000 patient-days.[12] 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 surgical unit (lower ADE incidence than medical unit[58]) was included in the study mentioned. Our result is lower than the study finding of 49.5% in Uganda.[59] This might be a difference in disease patterns and seasonal variation.

The causal relationship between the drug and the event as measured by the Naranjo algorithm was 26.72% definite, 60.34% probable, and 12.93% possible, which is comparable with a prospective

Table 9
Preventability of adverse drug events (ADEs) based on modified Schumock and Thornton preventability criteria.

Modified Schumock and Thornton preventability criteria		Frequency	%
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

* Definitely preventable.
† Probably preventable.
‡ Nonpreventable.

Table 10
Patient-related factors associated with adverse drug event (ADE) occurrence.

Variable		ADE occurrence*		Total*	COR (95% CI)	*P* value	AOR (95% CI)	*P* value
		No	Yes					
Sex	Male	116 (36.4)	42 (13.2)	158 (49.5)	1			
	Female	118 (37)	43 (13.5)	161 (50.5)	1.006 (0.613–0.653)	0.98		
Residence	Rural	163 (51.1)	62 (19.4)	225 (70.5)	1			
	Urban	71 (22.3)	23 (7.2)	94 (29.5)	0.852 (0.490–1.482)	0.57		
Educational status	Uneducated	153 (48)	65 (20.4)	218 (68.3)	1		1	
	Educated	81 (25.4)	20 (6.3)	101 (31.7)	0.581 (0.329–1.027)	0.062	0.614 (0.318–1.185)	0.146
Alcohol consumption	No	167 (52.4)	65 (20.4)	232 (72.7)	1			
	Yes	67 (21)	20 (6.3)	87 (27.3)	0.767 (0.431–1.364)	0.366		
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 (0.521–2.98)	0.620		
Age, y	18–35	97 (30.4)	26 (8.2)	123 (38.6)	1		1	
	36–50	68 (21.3)	24 (7.5)	92 (28.8)	1.317 (0.697–2.49)	0.396		
	51–65	41 (12.9)	26 (8.2)	67 (21)	2.366 (1.23–4.55)	0.010	1.197 (0.490–2.924)	0.693
	≥66	28 (8.8)	9 (2.8)	37 (11.6)	1.199 (0.5–2.853)	0.681		
Occupation	Student	42 (13.2)	9 (2.8)	51 (16)	1			
	Government employee	11 (3.4)	2 (0.6)	13 (4.1)	0.848 (0.160–4.506)	0.847		
	Merchant	16 (5)	7 (2.2)	23 (7.2)	2.042 (0.651–6.41)	0.221		
	Self-employed	18 (5.6)	3 (0.9)	21 (6.6)	0.778 (0.188–3.213)	0.728		
	Farmer	107 (33.5)	48 (15)	155 (48.6)	2.093 (0.944–4.64)	0.069		
	Unemployed	40 (12.5)	16 (5)	56 (17.6)	1.867 (0.741–4.70)	0.186		

AOR = adjusted odds ratio; COR, crude odds ratio.
* Values are presented as n (%).

Table 11
Disease-related factors associated with adverse drug event (ADE) occurrence.

Variable		ADE occurrence*		Total*	COR (95% CI)	*P* value	AOR (95% CI)	*P* value
		No	Yes					
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 (0.671–1.89)	0.653		
Genitourinary system disease	No	166 (52)	62 (19.4)	228 (71.5)	1			
	Yes	68 (21.3)	23 (7.2)	91 (28.5)	0.906 (0.520–1.58)	0.726		
Blood and immune disease	No	175 (54.9)	58 (18.2)	233 (73)	1		1	
	Yes	59 (18.5)	27 (8.5)	86 (27)	1.381 (0.802–2.38)	0.245	1.611 (0.856–3.032)	0.139
Endocrine and metabolic disease	No	191 (59.9)	59 (18.5)	250 (78.4)	1		1	
	Yes	43 (13.5)	26 (8.2)	69 (21.6)	1.957 (1.11–3.45)	0.020	1.276 (0.543–2.998)	0.577
Digestive system disease	No	199 (62.4)	57 (17.9)	256 (80.3)	1		1	
	Yes	35 (11)	28 (8.8)	63 (19.7)	2.793 (1.57–4.98)	< 0.001	2.838 (1.446–5.571)	0.002
Respiratory system disease	No	187 (58.6)	70 (21.9)	257 (80.6)	1			
	Yes	47 (14.7)	15 (4.7)	62 (19.4)	.853 (0.448–1.622)	0.627		
Nervous system disease	No	185 (58)	70 (21.9)	255 (79.9)	1			
	Yes	49 (15.4)	15 (4.7)	64 (20.1)	.809 (0.426–1.535)	0.517		
Circulatory system disease	No	121 (37.9)	29 (9.1)	150 (47)	1		1	
	Yes	113 (35.4)	56 (17.6)	169 (53)	2.068 (1.23–3.47)	0.006	2.669 (1.456–4.889)	0.001
LOS, d	1–7	48 (15)	6 (1.9)	54 (16.9)	1		1	
	8–14	93 (29.2)	23 (7.2)	116 (36.4)	1.978 (0.755–5.18)	0.165	2.112 (0.77–25.773)	0.145
	15–21	43 (13.5)	24 (7.5)	67 (21)	4.465 (1.67–11.95)	0.003	3.928 (1.388–11.121)	0.010
	≥22	50 (15.7)	32 (10)	82 (25.7)	5.12 (1.965–13.34)	0.001	4.348 (1.543–12.254)	0.005

AOR = adjusted odds ratio; COR = crude odds ratio; LOS = length of stay.
* Values are presented as n (%).

study in Spain.[60] A study in India showed most of the reactions had probable relation to the suspected medications (51%) followed by possible relation (49%).[61] Another study in India reported 61% probable and 39% possible ADEs.[62] Most of the ADEs were probable (35.5%) and possible (31.4%), as reported in Pakistan.[63] However, fewer definite and probable events were reported: definite (2%) and probable (27%) in Uganda.[55] This might be because fewer laboratory data were used on the assessment of ADEs, as reported by the authors.

In our study, the most frequent system organ influenced by ADEs are in line with other recent studies[55,62,64–66]; that is, ADEs affecting gastrointestinal (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 system (3.45%), and immune system (0.86%) were less frequently involved.

Using the modified Hartwig Severity Assessment Scale, it was seen that 61 (52.59%) were moderate, 43 (37.07%) were mild, and 12 (10.34%) were severe ADEs. Thus, most of the ADEs detected were moderate in severity. Comparable to this, 61.4% moderate events were reported in India using a similar assessment scale.[67] Most (62.07%) ADEs observed were preventable (26.72% definitely preventable and 35.35% probably preventable). In line with this, another study in India used similar criteria and reported 66.7% pre-

Table 12
Drug-related factor associated with adverse drug event (ADE) occurrence.

Variable		ADE occurrence*		Total*	COR (95% CI)	*P* value	AOR (95% CI)	*P* value
		No	Yes					
Antibiotics	No	114 (35.7)	43 (13.5)	157 (49.2)	1			
	Yes	120 (37.6)	42 (13.2)	162 (50.8)	.928 (0.565–1.525)	0.768		
Cardiovascular medicines	No	126 (39.5)	39 (12.2)	165 (51.7)	1		1	
	Yes	108 (33.9)	46 (14.4)	154 (48.3)	1.376 (0.836–2.264)	0.209	1.274 (0.570–2.847)	0.555
Antiviral agents	No	220 (69)	78 (24.5)	298 (93.4)	1			
	Yes	14 (4.4)	7 (2.2)	21 (6.6)	1.410 (0.549–3.622)	0.475		
Anticoagulant agents	No	197 (61.8)	70 (21.9)	267 (83.7)	1			
	Yes	37 (11.6)	15 (4.7)	52 (16.3)	1.141 (0.590–2.205)	0.695		
Antidyslipidemia agents	No	196 (61.4)	70 (21.9)	266 (83.4)	1			
	Yes	38 (11.9)	15 (4.7)	53 (16.6)	1.105 (0.573–2.132)	0.765		
Anti-TB agents	No	210 (65.8)	66 (20.7)	276 (86.5)	1		1	
	Yes	24 (7.5)	19 (6)	43 (13.5)	2.519 (1.299–4.885)	0.006	2.523 (1.064–5.982)	0.036
Vitamins	No	181 (56.7)	60 (18.8)	241 (75.5)	1		1	
	Yes	53 (16.6)	25 (7.8)	78 (24.5)	1.423 (0.814–2.486)	0.215	0.874 (0.364–2.101)	0.764
Antidiabetes agents	No	219 (68.7)	73 (22.9)	292 (91.5)	1		1	
	Yes	15 (4.7)	12 (3.8)	27 (8.5)	2.400 (1.074–5.363)	0.033	2.198 (0.436–11.071)	0.340
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)	0.465		
Antiseizure agents	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)	0.357		
Antiplatelet agents	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)	0.836		
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)	0.996		
Gastrointestinal medicines	No	158 (49.5)	47 (14.7)	205 (64.3)	1		1	
	Yes	76 (23.8)	38 (11.9)	114 (35.7)	1.681 (1.012–2.792)	0.045	0.928 (0.462–1.864)	0.834
No. of medications	1-3	95 (29.8)	26 (8.2)	121 (37.9)	1		1	
	4-6	117 (36.7)	38 (11.9)	155 (48.6)	1.187 (.673–2.093)	0.554		
	≥7	22 (6.9)	21 (6.6)	43 (13.5)	3.488 (1.666–7.301)	0.001	0.726 (0.272–1.940)	0.524
Medication error found	No	157 (49.2)	44 (13.8)	201 (63)	1		1	
	Yes	77 (24.1)	41 (12.9)	118 (37)	1.900 (1.146–3.149)	0.013	1.526 (0.859–2.714)	0.150

AOR = adjusted odds ratio; COR = crude odds ratio; TB = tuberculosis.
* Values are presented as n (%).

ventable events.[61] Kiguba et al[55] in Uganda found 54% preventable events (definite 2% and probable 52%), Geer et al[65] in India found 81.58% preventable events (definite 13.15% and probable 68.42%), Jayanthi et al[62] in India found 56% probably preventable events, Giardina et al[64] in Italy found 75.8% preventable events (probable 69.4% and definite 6.4%). In contrary to present study, Benkirane et al[68] in Morocco reported 70% of ADEs as nonpreventable. The discrepancy might be the authors did not use prevention probability scales rather defined ADRs as nonpreventable. In the current study, more than half of ADEs observed were preventable; it is high time to reinforce large-scale efforts to redesign safer, higher quality health care systems to adequately tackle the problem, targeting the prescribing and monitoring stages for prevention.

Regarding the medication classes accountable for ADEs, antibiotics, anti-TB agents, diuretics, steroids, anticoagulants, cardiovascular drugs, and analgesics have been most frequently reported in the literature.[12,55,65,66,69] In our study, diuretics (26.47%), antibiotics (16.67%), anti-TB agents (14.71%), cardiovascular drugs (10.78%), and anticoagulants (8.82%) were the most commonly implicated drug classes leading to the occurrence of ADEs.

Multivariate analysis indicated that length of hospital stay, use of anti-TB agents, diseases of the circulatory system, diseases of the digestive system, and taking medication at admission independently predicted the occurrence of ADEs in this study. The discrimination ability of the model was assessed using the area under the receiver operating characteristic, which was 75.2% (95% CI, 68.9%-81.5%).

Patients who stayed more than 2 weeks in hospital were 4 times more likely to experience ADEs when compared with patients who stayed less than a week. Similar finding was reported in other studies.[29,66,70,71] Also, Tangiisuran et al[48] reported length of hospital stay ≥12 days was significantly associated with ADE occurrences (OR, 2.3; 95% CI, 1.4–3.8).

Among identified risk factors for ADEs, disease-related factors were described in a previous study.[7] In our study, patients with diseases of circulatory and digestive system were about 3 times more likely to experience ADEs than patients without these disease condition. This correlates with the previous study by Urbina and colleagues,[72] who 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 ADE occurrence. Other related findings were also reported.[71] If the liver (a digestive system) functions less optimally, drugs are not readily metabolized and excreted and this leads to many drugs staying in the system much longer, the net result being the prolongation of pharmacodynamic effects and occurrence of ADEs.[73]

Patients receiving anti-TB agents were 2.5 times more likely to experience ADEs than patients who were not taking anti-TB agents. Marra et al[74] reported anti-TB agents independently associated with ADE occurrence. The use of multidrug regimens and over prolonged periods in TB treatment might be the reason.[75]

Taking medication during admission was found to have an association with the occurrence of ADEs. Nguyen et al[76] 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 the occurrence of ADEs. Also, Tangiisuran et al[48] 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 ($P < .001$).

Table 13
Previous medication and medical history associated with adverse drug event (ADE) occurrence

Variable		ADE occurrence*		Total*	COR (95% CI)	*P* value	AOR (95% CI)	*P* value
		No	Yes					
History of medication use during the past 3 mo	No	125 (39.2)	28 (8.8)	153 (48)	1		1	
	Yes	109 (34.2)	57 (17.9)	166 (52)	2.335 (1.388–3.927)	0.001	1.018 (0.354–2.927)	0.974
Taking medication during admission	No	171 (53.6)	40 (12.5)	211 (66.1)	1		1	
	Yes	63 (19.7)	45 (14.1)	108 (33.9)	3.054 (1.825–5.109)	< 0.001	3.09 (1.766–5.406)	< 0.001
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)	0.259		
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 (0.47–2.628)	0.809		
Antidiabetic drugs history	No	221 (69.3)	77 (24.1)	298 (93.4)	1		1	
	Yes	13 (4.1)	8 (2.5)	21 (6.6)	1.766 (0.705–4.424)	0.225	0.207 (0.015–2.839)	0.238
Cardiovascular medicines history	No	182 (57.1)	58 (18.2)	240 (75.2)	1		1	
	Yes	52 (16.3)	27 (8.5)	79 (24.8)	1.629 (0.939–2.827)	0.082	0.665 (0.306–1.448)	0.305
Previous medical condition of the 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 (0.768–2.27)	0.315		
Previous medical condition of endocrine and metabolic systems	No	220 (69)	74 (23.2)	294 (92.2)	1		1	
	Yes	14 (4.4)	11 (3.4)	25 (7.8)	2.336 (1.016–5.37)	0.046	1.765 (0.681–4.574)	0.242
Previous infectious disease	No	203 (63.6)	68 (21.3)	271 (85)	1		1	
	Yes	31 (9.7)	17 (5.3)	48 (15)	1.637 (0.853–3.143)	0.138	0.787 (0.302–2.048)	0.623
Hospitalization during the 3 mo before the study period	No	187 (58.6)	56 (17.6)	243 (76.2)	1		1	
	Yes	47 (14.7)	29 (9.1)	76 (23.8)	2.06 (1.188–3.574)	0.010	1.097 (0.541–2.225)	0.797

AOR = adjusted odds ratio; COR = crude odds ratio.
* Values are presented as n (%).

The well-studied risk factor that has been reported in several previous reports,[28,29,55,66,76] the 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 a confounder. From patient-related factors, an age range of 51 to 65 years had an association with the occurrence of ADEs in univariate analysis. Elderly patients are at high risk for ADEs because drugs are less likely to be studied extensively in elderly, and drug absorption and metabolism are more variable in this group.[77] Female patients have greater risk of developing an ADE, compared with male patients, particularly seen with hepatotoxicity and ADEs caused by psychotropic drugs.[77] Consistent with this, the hepatotoxicity observed was 5 out of 8 (62.5%) in women and 3 out of 8 (37.5%) in men in our study. But the ADEs caused by the psychotropic drug chlorpromazine were 2 out of 2 (100%) in men.

Limitations and strengths

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 supratherapeutic range and administration of placebo to see the reappearance of the adverse event, to ascertain ADE causality in addition to other scores. But, these are not performed in our setting, which overestimates or underestimates the scores. In addition, the single-center study design may limit the generalizability of the finding.

The strengths of this study are the ADEs were identified by prospective follow-up of the admitted patients, the ADE causality was established by standard tool Naranjo algorithm, and independent predictors of in hospital ADE occurrence were determined.

Conclusions

The incidence of ADEs identified in this study was consistent with the published data. One in every 4 patients admitted in the ward experienced ADEs during their hospital stay. Anti-TB agents, diseases of the circulatory and digestive systems, taking medication during admission, length of hospital stay 15 to 21 days, and length of hospital stay 22 days or more were independent predictors of the occurrence of ADEs.

Most ADEs were moderate in severity. About 2 out of 3 cases were judged as either moderate or severe. About two-third of ADEs identified were deemed probably or definitely preventable.

Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Acknowledgments

This study was sponsored by Jimma University, Ethiopia. The funder had no role in the study design, data collection and analysis, interpretation of data, decision to publish, or preparation of the manuscript.

The authors thank the Jimma University Institute of Health for giving us the chance to conduct this research. Our thanks extend to all data collectors and health care professionals at for their friendly work.

The analysis was conceptualized by T. Sahilu, M. Getachew, and T. Melaku. Data collection was managed by T. Sahilu and data analysis was conducted by T. Sahilu, M. Getachew, T. Melaku, and T. Sheleme. T. Sahilu drafted the manuscript. All authors (T. Sahilu, M. Getachew, T. Melaku, and T. Sheleme) participated in editing, feedback, and revisions. All authors read and approved the manuscript.

References

1. U.S. Agency for International Development. Management Sciences for Health and World Health Organization. Drug and Therapeutics Committee Training Course. 2007.
2. Food, Medicine and Healthcare Administration and Control Authority of Ethiopia. *Guideline for Adverse Drug Events Monitoring (Pharmacovigilance)*; 2014 *https://www.medbox.org/guideline-for-adverse-drug-events-monitoring-pharmacovigilance-ethiopia/download.pdf* accessed 27 feb 2019.
3. *National action plan for adverse drug event prevention*. 56Health UDo, Services H.. Washington (DC): Author; 2014.
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):476–485.
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. World Health Organization. 10 facts on patient safety. https://www.who.int/features/factfiles/patient_safety/en/ Accessed 16 Jan 2019.
9. 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.
10. 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):1539–1549.
11. Lisha J, Annalakshmi V, Maria J, Padmini D. Adverse Drug Reactions in Critical Care Settings: A Systematic Review. *Curr Drug Saf*. 2017;12(3):147–161.
12. 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.
13. 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).
14. 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):64–68.
15. 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.
16. 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):573–578.
17. Diaz Hernandez SH, Cruz-Gonzalez I. Incidence and Preventability of Medication Errors and ADEs in Ambulatory Care Older Patients. *Consult Pharm*. 2018;33(8):454–466.
18. 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.
19. 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).
20. 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).
21. 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):764–768.
22. 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.
23. 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):1407–1425.
24. Dalleur O, Beeler PE, Schnipper JL, Donze J. 30-Day Potentially Avoidable Readmissions Due to Adverse Drug Events. *J Patient Saf*. 2017;17(10).
25. 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.
26. 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.
27. 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.
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):62–66.
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):582–591.
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):1161–1168.
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):827–837.
32. 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).
33. 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.
34. Snyder RA, Fields W. A model for medication safety event detection. *Int J Qual Health Care*. 2010;22(3):179–186.
35. 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):306–314.
36. 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.
37. 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.
38. Griffin F.A., Resar R.K. IHI global trigger tool for measuring adverse events. Institute for Healthcare Improvement Innovation Series White Paper. 2009.
39. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clinical pharmacology and therapeutics*. 1981;30(2):239–245.
40. Varallo FR, Planeta CS, Herdeiro MT, Mastroianni PdC. Imputation of adverse drug reactions: Causality assessment in hospitals. *PloS one*. 2017;12(2) e.
41. Davies EC, Rowe PH, James S, Nickless G, Ganguli A, Danjuma M, et al. An investigation of disagreement in causality assessment of adverse drug reactions. *Pharmaceutical medicine*. 2011;25(1):17–24.
42. Mello MM, Greenberg Y, Senecal SK, Cohn JS. Case Outcomes in a Communication-and-Resolution Program in New York Hospitals. *Health Serv Res*. 2016;3:2583–2599.
43. Agbabiaka TB, Savović J, Ernst E. Methods for Causality Assessment of Adverse Drug Reactions. *Drug Safety*. 2008;31(1):21–37.
44. Murphy JFA. Medical Negligence Costs are Unsustainable. *Ir Med J*. 2018;111(6):765.
45. Belhekar MN, Taur SR, Munshi RP. A study of agreement between the Naranjo algorithm and WHO-UMC criteria for causality assessment of adverse drug reactions. *Indian J Pharmacol*. 2014;46(1):117–120.
46. Gauld R, Horsburgh S. Healthcare professional perspectives on quality and safety in New Zealand public hospitals: findings from a national survey. *Aust Health Rev*. 2014;38(1):109–114.
47. 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.
48. Tangiisuran B. Predicting adverse drug reactions in the hospitalised elderly [PhD Thesis]. *Brighton: University of Sussex*. 2009.
49. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm*. 1992;49:2229–2232.
50. Petrova G, Stoimenova A, Dimitrova M, Kamusheva M, Petrova D, Georgiev O. Assessment of the expectancy, seriousness and severity of adverse drug reactions reported for chronic obstructive pulmonary disease therapy. *SAGE open medicine*. 2017;5.
51. Bhimji S.S., Scherbak Y. Medication Errors.
52. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm*. 1992;27(6):538.

53. A PT, Badger J, LaRose E, Shirzadi E, Mahnke A, Mayer J, et al. Adverse Drug Event Discovery Using Biomedical Literature: A Big Data Neural Network Adventure. *JMIR Med Inform*. 2017;5(4).
54. 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.
55. 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).
56. 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):2150–2157.
57. 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):1414–1419.
58. 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).
59. 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):72–78.
60. 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.
61. 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.
62. 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).
63. Saqib A, Sarwar MR, Sarfraz M, Iftikhar S. Causality and preventability assessment of adverse drug events of antibiotics among inpatients having different lengths of hospital stay: a multicenter, cross-sectional study in Lahore, Pakistan. *BMC Pharmacol Toxicol*. 2018;19(1):018–0222.
64. 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).
65. 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;81:323–334.
66. 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.
67. 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.
68. 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.
69. 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):1373–1379.
70. 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.
71. 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).
72. 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):923–932.
73. Malangu N. *Pharmacokinetics and Adverse Effects of Drugs-Mechanisms and Risks Factors*. Introductory Chapter: Linkages between Pharmacokinetics and Adverse Effects of Drugs. IntechOpen; 2018.
74. 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):868–875.
75. 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):21–29.
76. 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).
77. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharm J*. 2014;22(2):83–94 Epub 02/24.