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

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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. 4 Hospital adverse events are an important source of morbidity and mortality in different countries and settings. 1,5 and represent an important item of expenditure for health care systems and their prevention could be associated with a relevant cost-saving. 1 They are among the leading causes of morbidity and hospitalization in health facilities. 6 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. 7 The systematic review done by Jolivot et al 8 reported that the incidence of ADEs in adult inpatients ranged from 0.37%

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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 patients13–15 and 7.9 to 30.6 per 1000 patient-days,15,16 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 al25 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 al28 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,29 length of hospital stay,30 comorbidity,31 inappropriate use of drugs, cardiovascular agents, and anti-infection treatments32 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 al32 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 Tool38 and the medication module of the Institute for Healthcare Improvement Global Trigger Tool39 for measuring ADEs was used to facilitate manual chart reviews and increase detection of ADEs. ADR causality was assessed by the Naranjo ADR probability scale40 because it was developed and validated for the assessment of ADRs40 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 criteria42 have been criticized for being subjective and imprecise.43 The Karch and Lasagna44 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 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 were used to facilitate ADE detection. 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, 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. 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, 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. The US Food and Drug Administration classifies an ADE as serious when it results in death, is life-threatening, prolongs hospitalization, results in persistent or significant incapacity, or results in a congenital anomaly. 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.

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 multicollinearity by collinearity diagnostics. Assumption of independence (adequacy of cells) was carried out by χ² 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 100.
- 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 participants 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
[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 1
Sociodemographic and clinical characteristics of study participants.

| Variable          | Frequency | %   |
|-------------------|-----------|-----|
| Sex               | Male      | 158 | 49.5 |
|                   | Female    | 161 | 50.5 |
| Age, y ≥66        |           | 67  | 21.0 |
|                  | 51–65     | 123 | 38.6 |
|                  | 36–50     | 92  | 28.8 |
|                  | 18–35     | 123 | 38.6 |
| 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 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 adverse drug reaction(s) | | 11 | 3.4 |
| Had history 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).

Table 2
The primary diagnosis of study participants.

| ICD-10 code | Diagnosis                                      | Frequency | %   |
|-------------|-----------------------------------------------|-----------|-----|
| I00-99      | 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) | %   |
|-------------|-----------------------------------------------|---------------------|-----|
| I00-99      | 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 anionemic agents | 78    | 24.5 |
| 6           | Electrolytes            | 59        | 18.5 |
| 7           | Antiplatelets           | 54        | 16.9 |
| 8           | Antidyalysisipemic 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          | Antithyroid agents      | 11        | 3.4  |
| 17          | Antithyroid agents      | 9         | 2.8  |
| 18          | Antipsychotic agents    | 9         | 2.8  |
| 19          | Antimalarials           | 6         | 1.9  |
| 20          | Anthistaminas           | 3         | 0.9  |

### 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 was 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%]).

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 tartrate (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)                                            |
| Endocrine and metabolic       | 25 (21.55)| Hyperkalemia\(^†\) (2 serious ADEs) 4 (3.5) | Furosemide (1)                                          |
|                               |           | Hypercalcemia 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), RHZ\(^†\) (1), insulin\(^†\) (5), gentamicin (1) |
|                               |           | Hyponatremia\(^†\) (1 serious ADE) 5 (4.3) | Furosemide (4), RHZ\(^†\) (1)                           |
|                               |           | Hyperglycemia 1 (0.9) | Desmethyl (1)                                           |
| Cardiovascular system         | 23 (19.83)| Hypotension 18 (15.52) | Furosemide (14), mannitol (1), metoprolol succinate (1), chlorpropamide (1), cimetidine (1) |
|                               |           | Second-degree atrioventricular block 1 (0.9) | Digoxin (1)                                             |
|                               |           | Cardiogenic shock 1 (0.9) | Furosemide + enalapril + metoprol succinate (1)         |
|                               |           | Hypovolemic shock 1 (0.9) | Furosemide (1)                                          |
|                               |           | Peripheral edema 1 (0.9) | Amiodipine (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), chlorpropamide (1), cotrimoxazole + zidovudine (1)                     |
|                               |           | Thrombocytopenia\(^†\) (1 serious ADE) 2 (1.7) | Amiodipine (1), UFH\(^†\) (1)                           |
|                               |           | Bictepenia (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)     | Cotrimoxazole (1), enalapril + furosemide + ceftriaxone (1), warfarin + UFH (1)         |
| Respiratory                   | 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%)           |                                                          |

\(^*\) Values are presented as n (%).
\(^†\) Serious ADEs (24 out of 116 [20.69%]).

### 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 drugs | 11 (10.78)    | Metoprol tartrate (1), digoxin (1), metoprol succinate (2), enalapril (6), propranolol (1) |
| Anticoagulant        | 9 (8.82)      | UFH (4), warfarin (5)    |
| Antidiabetic         | 6 (5.88)      | Insulin                  |
| Gastrointestinal drugs | 3 (2.94)  | Cimetidine (2), omeprazole (1) |
| Antiviral            | 2 (1.96)      | Zidovudine (2)           |
| Steroids             | 2 (1.96)      | Prednisolone (1), dexamethasone (1) |
| Antipsychatic        | 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               |
| Antihelmintic        | 1 (0.98)      | Ivermectin               |
| Total                | 102 (100)     |                           |

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

\(^†\) Serious ADEs (24 out of 116 [20.69%]).

\(^*\) Medications involved in serious ADEs.
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).

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 |

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

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 |
| Were preventative measures not prescribed or administered to the patient? | 3         | 2.59 |
| Total                                                | 44        | 37.93 |

† Definitely preventable.  
‡ Probably preventable.  
§ Nonpreventable.

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. ADEs led to additional medical costs, prolonged hospitalization, morbidity, and ascertainable disability worldwide. They are largely preventable and occur mostly at the prescribing stage of the medication use process. 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. 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. 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) was included in the study mentioned. Our result is lower than the study finding of 49.5% in Uganda. 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
study in Spain. A study in India showed most of the reactions had probable relation to the suspected medications (51%) followed by possible relation (49%). Another study in India reported 61% probable and 39% possible ADEs. Most of the ADEs were probable (35.5%) and possible (31.4%), as reported in Pakistan. However, fewer definite and probable events were reported: definite (2%) and probable (27%) in Uganda. This might be because fewer laboratorial 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; that is, ADEs affecting gastrointestinal (30.1%), endocrine and metabolic (21.5%), hematologic (12.9%), and cardiovascular system (19.8%) 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. 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 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   | 42 (13.2)    | 158     | (49.5)       | 1       |
|                     | Female         | 118   | 43 (13.5)    | 161     | (50.5)       | 1.006   |
|                     |                |       | (0.613–0.653)|         | 0.98        |         |
| Residence           | Rural          | 163   | 62 (19.4)    | 225     | (70.5)       | 1       |
|                     | Urban          | 71    | 23 (7.2)     | 94      | (28.5)       | 0.852   |
|                     |                |       | (0.490–1.482)|         | 0.57        |         |
| Educational status  | Uneducated     | 153   | 65 (20.4)    | 218     | (68.3)       | 1       |
|                     | Educated       | 81    | 20 (6.3)     | 101     | (31.7)       | 0.581   |
| Alcohol consumption | No             | 167   | 52 (14.9)    | 232     | (72.7)       | 1       |
|                     | Yes            | 67    | 21 (6.3)     | 87      | (27.3)       | 0.767   |
| Tobacco use         | No             | 216   | 67 (21.4)    | 293     | (91.8)       | 1       |
|                     | Yes            | 18    | 5.6 (16.3)   | 26      | (8.2)        | 1       |
| Age, y              | 18–35          | 97    | 30.4 (26.2)  | 123     | (38.6)       | 1       |
|                     | 36–50          | 68    | 21.3 (24.7)  | 92      | (28.8)       | 1       |
|                     | 51–65          | 41    | 12.9 (26.2)  | 67      | (21)         | 2.366   |
|                     | ≥66            | 28    | 8.8 (2.8)    | 37      | (11.6)       | 1       |
| Occupation          | Student        | 42    | 13.2 (4.2)   | 51      | (16)         | 1       |
|                     | Government employee | 11  | 3.4 (0.6)    | 13      | (4.1)        | 0.848   |
|                     | Merchant       | 16    | 5 (2.2)      | 21      | (7.2)        | 2.042   |
|                     | Self-employed  | 18    | 5.6 (3.9)    | 21      | (6.6)        | 0.778   |
|                     | Farmer         | 107   | 33.5 (48.1)  | 155     | (48.6)       | 2.093   |
|                     | Unemployed     | 40    | 12.5 (16)    | 56      | (17.6)       | 1.867   |

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   | 54 (16.9)    | 209     | (65.5)       | 1       |
|                     | Yes            | 79    | 24.8 (9.7)   | 110     | (34.5)       | 1.126   |
|                     |                |       | (0.671–1.89) |         | 0.653        |         |
| Genitourinary system disease | No | 166   | 52 (19.4)    | 228     | (71.5)       | 1       |
|                     | Yes            | 68    | 21.3 (7.2)   | 91      | (28.5)       | 0.906   |
|                     |                |       | (0.520–1.58) |         | 0.726        |         |
| Blood and immune disease | No | 175   | 54 (18.2)    | 223     | (73)         | 1       |
|                     | Yes            | 59    | 18.5 (8.5)   | 86      | (27)         | 1.381   |
|                     |                |       | (0.802–2.38) |         | 0.245        |         |
| Endocrine and metabolic disease | No | 191   | 59 (18.5)    | 250     | (78.4)       | 1       |
|                     | Yes            | 43    | 13.5 (8.2)   | 69      | (21.6)       | 1.957   |
|                     |                |       | (1.11–3.45)  |         | 0.020        |         |
| Digestive system disease | No | 199   | 62.4 (17.9)  | 256     | (80.3)       | 1       |
|                     | Yes            | 35    | 11 (8.8)     | 63      | (19.7)       | 2.793   |
|                     |                |       | (1.57–4.98)  | < 0.001 | 2.838        | 0.002   |
| Respiratory system disease | No | 187   | 58.6 (21.9)  | 257     | (80.6)       | 1       |
|                     | Yes            | 47    | 14.7 (4.7)   | 62      | (19.4)       | .853    |
|                     |                |       | (0.448–1.622)|         | 0.627        |         |
| Nervous system disease | No             | 185   | 58 (21.9)    | 255     | (79.9)       | 1       |
|                     | Yes            | 49    | 15.4 (4.7)   | 64      | (20.1)       | .809    |
|                     |                |       | (0.426–1.535)|         | 0.517        |         |
| Circulatory system disease | No | 121   | 37.9 (9.1)   | 150     | (47)         | 1       |
|                     | Yes            | 113   | 35.4 (17.6)  | 169     | (53)         | 2.068   |
|                     |                |       | (1.23–3.47)  | 0.006   | 2.669        | 0.001   |
| LOS, d              | 1–7            | 48    | 15 (1.9)     | 54      | (16.9)       | 1       |
|                     | 8–14           | 93    | 29.2 (7.2)   | 116     | (36.4)       | 1.078   |
|                     |                |       | (0.755–5.18) | 0.165   | 2.112        | 0.045   |
|                     | 15–21          | 43    | 13.5 (7.5)   | 67      | (21)         | 4.465   |
|                     | 22             | 50    | 15.7 (12)    | 82      | (25.7)       | 5.12    |

AOR = adjusted odds ratio; COR, crude odds ratio; LOS, length of stay.

* Values are presented as n (%).
ventable events.\textsuperscript{51} Kiguba et al.\textsuperscript{55} in Uganda found 54% preventable events (definite 2% and probable 52%), Geer et al.\textsuperscript{55} in India found 81.58% preventable events (definite 13.15% and probable 68.42%), Jayanthi et al.\textsuperscript{62} in India found 56% probably preventable events, Giardina et al.\textsuperscript{64} in Italy found 75.8% preventable events (probable 69.4% and definite 6.4%). In contrary to present study, Benkirane et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{29,66,70,71} Also, Tangiisuran et al.\textsuperscript{48} reported length of hospital stay $\geq$ 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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{75}

Taking medication during admission was found to have an association with the occurrence of ADEs. Nguyen et al.\textsuperscript{59} 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.\textsuperscript{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 ($P < .001$).
The well-studied risk factor that has been reported in several previous reports, 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. Female patients have greater risk of developing an ADE, compared with male patients, particularly seen with hepatotoxicity and ADEs caused by psychotropic drugs. 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.
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