ORIGINAL RESEARCH

Prevalence, Incidence, and Characteristics of Adverse Drug Reactions Among Older Adults Hospitalized at Mbarara Regional Referral Hospital, Uganda: A Prospective Cohort Study

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Background: Adverse drug reactions (ADRs) are associated with significant clinical and economic effects. Among the elderly population, the risk for ADRs is even higher. Data of ADR prevalence and incidence among the elderly population in Uganda and many low- and middle-income countries are lacking.

Objective: This study determined the prevalence, incidence, and characteristics of ADRs among hospitalized elderly patients at Mbarara Regional Referral Hospital (MRRH), Uganda.

Methods and Materials: We conducted a prospective cohort of older adults admitted to medical, oncology, and surgery wards at MRRH for consecutive 6 months. The primary data were obtained by interviewing patients and caregivers and reviewing patient medication charts, taking vital signs, and physical examinations. We used Edwards and Aronson's definition of ADR and the Naranjo ADR Causality Scale. We conducted descriptive statistics and the Kolmogorov–Smirnov test using SPSS Version 23.0.

Results: We studied a total of 523 older adults 60 to 103 years of age. During their hospital stay, 256 (48.9%) of the patients experienced at least one ADR. A total of 365 ADRs were identified during 4702 person-days of follow-up. The incidence of ADRs was 78 ADRs/ 1000 person-days. ADRs affecting the gastrointestinal tract were the most frequently (40.6%) identified categories. Probable and type A ADRs accounted for 260 (71.2%) and 305 (83.6%) of the total incidents, respectively. Overall, 237 (64.9%) of the ADRs were rated as mild, whereas 10 (2.8%) of them as severe. Lastly, 165 (45.2%) of the ADRs were categorized as preventable.

Conclusion: Almost half of the hospitalized patients aged 60 to 103 years experienced at least one ADR during their hospital stay, which is higher than has been previously documented. Almost three-thirds of the ADRs were probable, about 4 out of 5 were type A and almost two-thirds were mild. Nearly half of the ADRs were preventable.

Keywords: prevalence, incidence, mechanism, severity, preventability, adverse drug reaction, elderly, inpatients

Introduction

An adverse drug reaction (ADR) may be defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product.[1] Both the United Nations and Ugandan Ministry of Gender, Labour and Social Development define the elderly as the age group of 60 years and older.[2,3] The

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life expectancy in Uganda has increased from 44 years in 1995 to 63 years in 2019.[4] Additionally, global estimates predict that the proportion of the population 60 years or older will nearly double from the 2015 levels of 12% to 22% in 2050. The majority (80%) of these will be living in low- and middle-income countries.[5]

Elderly people undergo various physiological and other body changes that alter their pharmacokinetics and pharmacodynamics of drugs making them highly susceptible to experience ADRs. Frail patients of 60 years and older experience a significantly higher incidence of ADRs.[6,7] Moreover, the common occurrence of multiple chronic diseases in the elderly necessitates polypharmacy, which increases the risk of ADRs by multiplying the probability of drug interactions.[8–11]

Systematic reviews that involved hospitalized older patients across the globe reported ADR prevalences of 11.5–24%.[12–15] A study conducted in the US and another from Ethiopia as well as a systematic review that included many studies across the world showed that about 10% of hospital admissions worldwide are related to ADRs.[16–18] In the US, approximately 100,000 emergency hospital admissions of older adults were attributed to ADRs every year.[19] In UK, a projected annual cost of 847 million US\$ and fatality of 0.15% was attributed to ADR-related hospital admissions.[20]

The safety data collected during the premarketing phase are inadequate due to the shorter study period, and the omission of unique groups of patients including the elderly.[21] The routine ADR reporting system is poor at identifying patient safety incidents, particularly those resulting in harm.[16] The hospital reporting systems significantly underestimate the incidence of ADRs in older populations, up to 100% under-reporting rate in the UK[16,22] and 77.2% in Uganda.[23] Thus, information about infrequent but severe ADRs as well as chronic toxicity and drug interactions often remains concealed. To this effect, pharmacovigilance studies are crucial for the identification of rare but serious ADRs among the elderly population.[24]

The classes of medications associated with ADRs are those that are commonly used during hospitalization.[19] The most commonly implicated drug classes in ADRs among hospitalized older patients include cardiovascular agents,[9,14,25–32] drugs acting on the nervous system (particularly NSAIDs, opioids, anticonvulsants, and antipsychotics),[9,14,27,29,31–33] anti-infective agents[25–27,30,33] and antineoplastic agents.[31,33,34]

ADRs are difficult to detect in older patients.[35] There are numerous methods available to evaluate the likelihood that observed adverse events are due to a particular drug.[36] The Naranjo algorithm, which is among the most commonly used algorithms, has a high correlation and agreement of ADR scores with the other commonly used methods like Kramer et al.[36] Another recent study also showed that both the WHO causality rating criteria and the Naranjo algorithm showed similar causality ratings.[37] In order to improve the identification of ADR in older adults, it is recommended for clinicians to have a high suspicion index for ADRs, as part of the differential diagnoses.[38]

The 2014 Ugandan National Housing and Population census estimated the elderly population (≥60 years) at over 1.2 million (3.7%).[39] The Ugandan elderly population was projected to be 1.6 million (5%) in 2019 and to 5.5 million by 2050.[2] Two studies from Uganda reported prevalences of 49.5%[40] and 25%[41] for suspected hospital-acquired ADRs. However, neither of the studies reported the prevalence of ADR among the older adult sub-group.

Previous study in Uganda reported up to half of the general adults experienced ADRs during hospitalization.[40] However, evidence of ADR prevalence and incidence specifically among the elderly inpatient population in low- and middle-income countries[12] including Uganda, more so from prospective cohort studies, is lacking. We, therefore, conducted a study among elderly inpatients at Medical, Oncology, and Surgical Departments at Mbarara Regional Referral Hospital to determine the prevalence and incidence of suspected ADRs. We also rated the causality of the suspected ADRs and characterized them by body system affected, causality, mechanism of occurrence, severity, preventability, and suspected causative drugs of the ADRs.

Methods and Materials
Study Setting and Period
This study was conducted at Mbarara Regional Referral Hospital (MRRH), a government-owned referral hospital, which is the largest public hospital in southwest Uganda with a 600-bed capacity. Currently, the hospital serves a population of over four million people in its catchment area including the districts of Mbarara, Bushenyi, Ntungamo, Kiruhura, Ibanda, Buhweju, Rubirizi, Mitooma, and Isingiro. The hospital also receives patients from Kabale, Masaka, Fort Portal, and neighboring countries like Rwanda and Tanzania. The hospital consists of the following wards: Emergency and Critical Care,

Oncology, Medicine, Surgery, Gynecology and Obstetrics, Psychiatry, Pediatrics, and TB, in addition to several outpatient clinics.[42] Most of the hospital services, in all units, are attended by postgraduate students and senior staff of Faculty of Medicine of Mbarara University of Science and Technology. The current study was conducted from 9th of November 2020 to 7th of May, 2021 for 6 consecutive months.

Study Design

We conducted a prospective observational study.

Study Population

All patients 60 years and older that were admitted to Medical, Oncology, and Surgery wards of MRRH during the study period who gave their informed consent were considered for sampling. We excluded patients suspected or confirmed of poisoning or overdose with medications before admission. We also excluded patients that died or were discharged in less than 48 hours of admission as well as those with pertinent laboratory and diagnostic test results not available within 48 hours of admission. We also excluded patients who were unable to make an effective interview: unconscious or in any level of coma, acute psychiatric condition, and hearing or speech impairment.

Sample Size

We used EPI INFO[TM] Version 7.2.3.1 employing Kelsey's formula at a confidence level of 95% and power of 80%; and prevalence from the previous study in a similar setting,[26] the minimum sample size required was 500 for polypharmacy and between 84 and 500 for all other variables. We added 10% for possible non-response, incomplete patient files, and too early discharge of the patients, resulting in a target sample size of 556. Thus, in practice, we studied 523 patients achieving a 2-sided margin of error of less than 5% (4.3%).

Sampling Technique

Every day during the study period, in each ward, the files of newly admitted patients were assigned consecutive numbers starting from one in a sequence of times of their admission. From MRRH records of the previous year, 1st of November 2019 to 30th of April 2020, an estimate of 1150 patients 60 years and older were admitted at Medical, Oncology, and Surgery wards. Thus, to achieve a sample of 556, we used simple random sampling to select half of the daily admissions in each ward. We generated the random numbers using MS-Excel version 2016. Every patient had an equal chance of selection of 50%. We continued the same procedure until the target sample size of 556 was achieved.

Data Collection

The principal investigator trained the research team consisting of four research assistants who pharmacists pursuing master's program in clinical pharmacy and two physicians who were final year master of medicine students in internal medicine. A pre-test study was conducted and data collection tools modified based on the experiences. Every week from Monday to Saturday between 9:00 am and 5:00 pm, we selected patients and obtained informed consent from each selected patient before enrollment.

First, on the day of enrollment, the trained research assistants collected data using the pre-tested structured questionnaire from patients and caregivers. These data included socio-demographics characteristics, social drug use, medical and medication history, drug allergies, use of over-the-counter and herbal medicines.

Second, we reviewed patients' medical records for working diagnosis, previous allergies, and clinical and laboratory data within 48 hours of admission. The data on previous and current medications were obtained from the patient's clinical notes, treatment sheets, drug administration charts, pill count validation, inspecting for leftover medicines, and through interviewing the patient/caregiver or ward staff.

Third, every day during their hospital stay, patients were interviewed, and their information was updated. Results of diagnostic and laboratory tests as well as vital statistics, such as body weight, height, body temperature, blood pressure, respiratory rate, pulse rate and pain scale, were documented at admission and followed up until discharge. The team's physicians helped in conducting physical assessments, and interpreting clinical, laboratory and diagnostic data when necessary.

Then, the principal researcher (TMY) monitored each patient for adverse-events. The team's physician (a senior physician) independently and blindly reviewed all cases with suspected adverse events and randomly selected 20% of those without suspected adverse events to replicate or even expand the principal researcher's detection. All adverse events suspected by the principal investigator and the physician were considered for ADR causality rating and discussion by the team.

Preliminary Review and Identification and Characterization of Suspected ADRs

On admission, all the patients were screened for any community acquired ADRs that were excluded from the final analysis. In this study, we defined hepatitis as an increase of AST or ALT value of at least 2 times the upper limit normal. CNS toxicity meant any nightmares, dizziness, insomnia, nervousness, lack of concentration, depression, suicidal ideation, or psychosis. Renal failure was defined as eGFR decline to less than 60 mL/min/1.73 m^2 or any increase of serum creatinine by 0.3mg/dL from baseline or reaching 1.5mg/dL. Hypotension was defined as systolic blood pressure <90mmHg or diastolic blood pressure <60 mmHg. We identified hypertension when systolic blood pressure was ≥140 mmHg or diastolic blood pressure ≥90mmHg. Extrapyramidal reaction was detected when one or more of dystonia, akathisia, parkinsonism, and tardive dyskinesia occurred. Hypoglycemia was defined as plasma glucose less than 55 mg/dL or 3 mmol/L with or without clinical symptoms. Constipation was defined as no bowel movement for at least 72 hours or less than three bowel movements per week with any two of the following features: straining, lumpy hard stools, the sensation of incomplete evacuation, use of digital maneuvers, the sensation of anorectal obstruction with 25% of bowel movements.[43,44] We used different methods to identify and characterize the identified ADRs.

We employed Edwards and Aronson's definition of ADR[1] as presented above. The known adverse reaction profile of each drug was evaluated based on Ugandan Clinical Guidelines (UCG, 2016), British National Formulary (BNP),[45] and Up-To-Date (2019) version 3.12.0.[44] ADRs were first suspected when there is a relationship between the time of drug administration and the onset and course of the adverse reaction while excluding other potential causes.[46]

Second, the rating of the causal relationship between an ADR and the suspected medication was done using the Naranjo ADR assessment scale.[47] We excluded all doubtful ADRs, whereas we considered those rated as possible, probable or definite for discussion and verification by the team of experts. The team of experts consisting of the principal investigator (senior clinical pharmacist), another senior pharmacist and a senior physician met daily to discuss the causality of the suspected ADRs and whenever consensus was not reached, a majority decision of the three members was applied.

Third, the principal investigator categorized the body system affected by ADRs using the International Statistical Classification of Diseases for Mortality and Morbidity Statistics (ICD-11 MMS).[48] The identified ADRs were categorized as type A (dose dependent, augmented pharmacological and predictable reactions) and type B (bizarre, dose independent and non-predictable reactions) according to the Rawlins and Thompson classification method[49] and the ABCDEF that added type C (dose and time dependent or chronic reactions), type D (delayed reactions), type E (withdrawal reactions), and type F (failure of therapy) to Rawlins and Thompson classification.[50]

Fifth, the severity of ADRs was determined by using the modified Hartwig and Siegel criteria, which has 7-items and 3 categories of severity: mild, moderate and severe ADRs.[51] Sixth, ADRs were assessed for preventability using 9-item Schumock and Thornton criteria which categorizes ADRs in to "definitely preventable", "probably preventable" or "not preventable".[52] Lastly, the medications implicated in the suspected ADRs were classified according to the WHO-Anatomical Therapeutic Chemical (ATC) classification,[53] whereas Lexicomp software was used to detect potential drug–drug interactions.

Data Analysis

The data were entered and cleaned by EpiInfo version 7.2.3.1 and then transferred to and analyzed by IBM Statistical Package for the Social Sciences (SPSS version 23.0 Inc., Chicago, Illinois). The prevalence of ADR was calculated by dividing the total number of patients that incurred at least one ADR by the total number of participants. We calculated the total person-days of the study by adding the hospital stay duration (days) of all participants. We calculated incidence by dividing the total number of ADR incidents by the total person-days. Descriptive statistics were employed to analyze the frequency and percentages of causality, types, mechanism, severity, and preventability of ADRs as well as the medications implicated in the suspected ADRs. The Kolmogorov–Smirnov test was used to determine the distribution of the variables. Continuous variables without normal distribution were summarized using the median and interquartile range.

Data Management and Quality Assurance

The collected data were checked daily for completeness and consistency by the principal investigator. The principal investigator supervised the data collection process daily

and gave necessary support to the research assistants who were final year master's students in clinical pharmacy. All the decisions of the principal researcher were discussed among the team of experts consisting of the principal investigator, the second clinical pharmacist and a physician, to reach a consensus. Completed individual patient data were anonymously passed to the data manager. Data were double-entered, cross-checked, and password-protected. The data collection tools were pre-tested among 25 older adults by the trained research assistants and revised accordingly.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki.[54] Approval to conduct the study was obtained from Mbarara University Institutional Research Ethics Committee (Reference No: MUREC 1/7) and Uganda National Council for Science and Technology (Reference No: HS992ES). We obtained site clearance to conduct the study from MRRH. We informed the participants about the study's objectives, benefits and risks, and

that their personal information would be kept confidential. We also explained their rights to autonomy, and the right to decline or to withdraw from the study. We obtained written informed consent from each participant before enrollment in this study. Data collection processes strictly adhered to Ministry of Health guidelines and Government directives for the prevention of COVID-19 transmission.

Results

Participants' Characteristics

Out of the 1185 older patients admitted during the study period, we approached 556 and enrolled 548 while eight declined to give consent. Later, 25 of them were discharged or died in less than 48 hours and thus, 523 were included in the final analysis with a response rate of 98.6% (Figure 1).

The study patients aged 60 to 103 years; with median age of 67 (62–76) years and 269 (51.4%) of them were males. The majority (338, 64.6%) had at least one comorbid condition. Almost one-third (30.0%) stayed in the
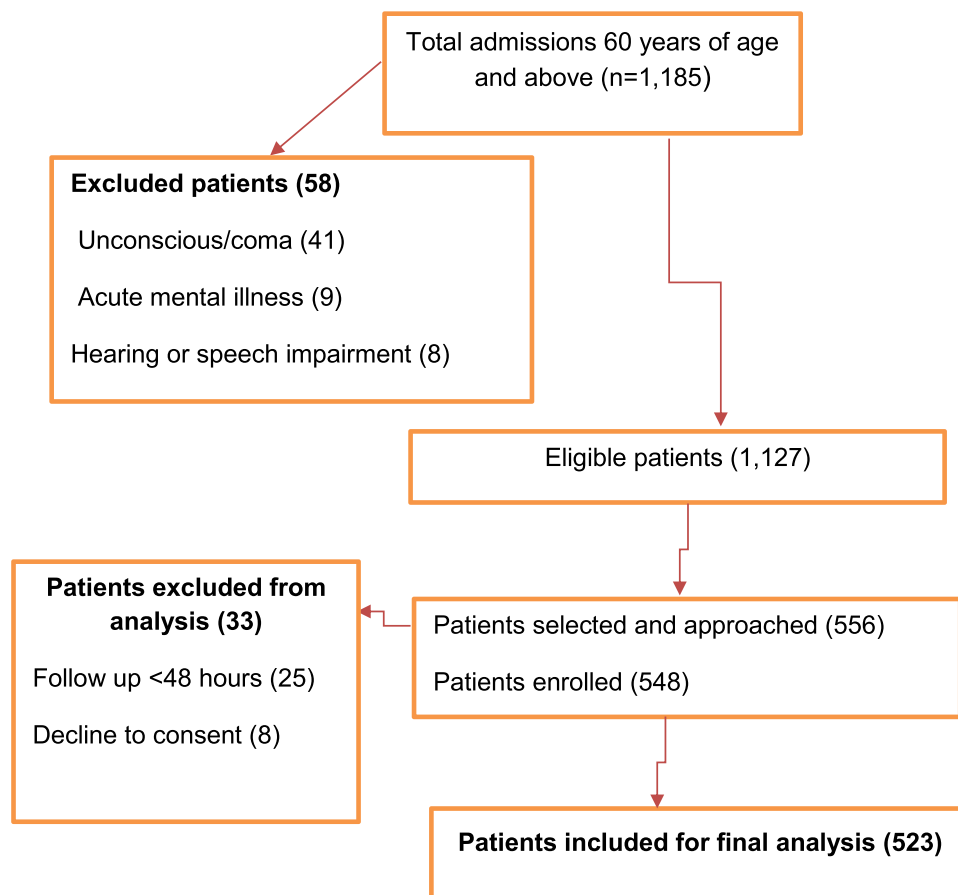

Figure 1 Study recruitment process of hospitalized older patients at MRRH, Uganda.

Table 1 Patient Characteristics of Older Adults 60 Years and Above Admitted at MRRH, Southwestern Uganda from November 2020 to May 2021

Variables	Categories	Frequency (%) (N=523)
Gender	Female Male	254 (48.6) 269 (51.4)
Age in years; median (IQR) =67 (62–76)	60–75 ≥75	356 (68.1) 167 (31.9)
Ward	Medical Surgery Oncology	262 (50.1) 163 (31.2) 98 (18.7)
Type of admission	Not Emergency Emergency	197 (37.7) 326 (62.3)
Medication use in previous 3 months	No Yes	49 (9.4) 474 (90.6)
Use of an herbal drug in previous 4 weeks	No Yes	251 (48.0) 272 (52.0)
Comorbidity	No Yes	185 (35.4) 338 (64.6)
Length of Hospital stay (days) Median (IQR): 8 (4–12)	≤5 5–10 ≥11	180 (34.4) 186 (35.6) 157 (30.0)

Abbreviation: IQR, interquartile range.

hospital for more than 10 days with a median (IQR) of 8 (4–12) days (Table 1). Using ICD-11 classification of diseases, infectious diseases (ICD class-01) were the most prevalent (39%) conditions diagnosed during the current hospitalization followed by neoplasms (36.1%) (Figure 2). Anti-infective agents were used by 373 (71.3%) of the patients followed by nervous system drugs that were used by 312 (59.7%) (Figure 3).

Prevalence and Incidence of Adverse Drug Reactions

A total of 256 patients out of 523 experienced at least one ADR incident during their hospital stay, giving a prevalence of 48.9% (95% C.I: 44.6%, 53.2%) (Figure 4). Out of the 256 patients that experienced ADRs, 171 (66.8%) experienced one ADR, while 61 (23.8%) and 24 (9.4%) of them incurred two, and three incidents of ADRs, respectively. The incidence of ADR was shown to be 78 ADRs/1000 person-days (Table 2).

Number of Adverse Drug Reactions

Causality Rating of the ADRs

By applying the Naranjo ADR causality rating scale, out of 365 ADRs, 260 (71.2%) were rated as probable, whereas 101 (28%) and 4 (0.8%) were rated as possible and definite ADRs, respectively.

Types of Adverse Drug Reactions Detected and the Body Systems Affected

Accounting for 40.6% of the totality, ADRs affecting the gastro-intestinal tract were the most frequently identified types followed by ADRs involving the central nervous system (20.5%), endocrine and metabolic system (8.8%), and cardiovascular system (8.5%). The most frequently detected specific ADRs were constipation,[42] nausea,[38] nausea and vomiting,[36] dizziness,[29] drowsiness,[16] hypotension,[16] and hypoglycemia[13] (Table 3).

Mechanism, Severity, and Preventability of the Suspected Adverse Drug Reactions

A total of 305 (83.6%) of the ADRs were categorized as "Type A" followed by 46 (12.6%) "Type B" and 6 (1.6%) 'Type C ADRs. On the other hand, 237 (64.9%) of the ADRs were mild, whereas 118 (32.3%) and 10 (2.8%) were moderate and severe, respectively. Out of the 10 patients that experienced severe ADRs, 4 died, 2 recovered with a complication and 4 recovered without a complication. Lastly, 165 (45.2%) of the ADRs were preventable; 107 (29.3%) of them being definitely preventable. There was a previous ADR or allergy to the drug in 47 (43.9%), and the drug was inappropriate in 39 (36.5%) of the definitely preventable ADRs. Monitoring tests were not performed in 22 (37.9%), and drug interaction was involved in 17 (29.3%) of the probably preventable ADRs (Table 4).

Potential Causative Drugs of the Adverse Drug Reactions

Out of the 365 ADRs detected, cardiovascular drugs and nervous system drugs were implicated in 76 (20.8%) and 75 (20.5%) of the ADRs, respectively. Sixty-three (84%) of the culprit nervous system drugs were analgesics. Constipation attributed to tramadol,[25] electrolyte disorders by furosemide,[14] and hypotension due to antihypertensives[10] were the most notable ADRs by these two classes of drugs. Antipsychotics were implicated in
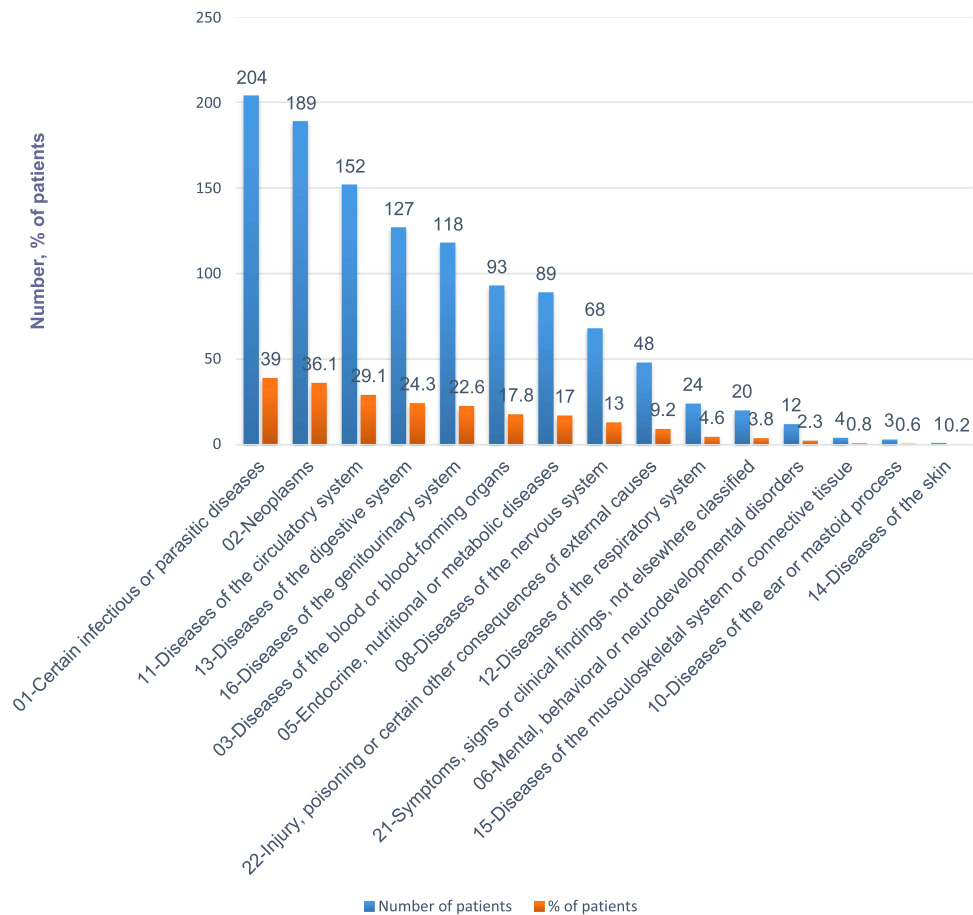
Figure 2 Documented medical, surgical, and oncologic conditions among older adults 60 years and above admitted at MRRH, southwestern Uganda from November 2020 to May 2021.

four episodes of extrapyramidal reactions. Anti-infectives and antineoplastic and immunomodulating agents were implicated for 71 (19.4%) and 69 (18.9%) of the ADRs, respectively. Ceftriaxone alone contributing to 51 ADRs by anti-infectives and docetaxel to 12 ADRs from antineoplastic agents (Table 5).

Discussion

In the current study, we achieved a very high (98.6%) response rate. This may be attributed to absence of any risk associated with the study and an extensive explanation about the procedures, risks and benefits of the study before consent was requested. Almost half (256, 48.9%) of the participants encountered at least one ADR incident during their hospital stay. The current prevalence of ADRs in hospitalized older patients is considerably higher compared to prevalences from high-income countries including 6% in Canada,[55] 6.5% in Italy,[56] 13% in the UK,[27] 15% in Japan,[9] 26% in Ireland,[29] 25.9% in Germany[57] and 26.2% in Australia.[15] The current prevalence is also higher

compared to studies from middle-income countries including 10.7% in Pakistan,[26] 18% in Brazil,[58] 30% in Malaysia,[28] and 32% in India.[59]

The current prevalence is also higher than the mean prevalence of ADR ranging from 11.5% to 24% reported by previous systematic reviews.[13,14,18] All of the previous studies conducted in this setting are from middle income or high-income countries. This may be explained by absolute lack of active clinical pharmacovigilance in our setting as compared to the previous studies as none of them was conducted in low-income country or in sub-Saharan Africa. To this effect, 45.2% of the reported ADRs could have been prevented if physicians or pharmacists daily checked for and avoided the known risk factors of ADRs like a drug that had previously caused allergy or ADR and inappropriate medications, or if they regularly reported the safety monitoring tests. Studies in Uganda showed many challenges in the pharmacovigilance system including lack of training and unfamiliarity with the pharmacovigilance system, lack of necessary funding, inadequate number of
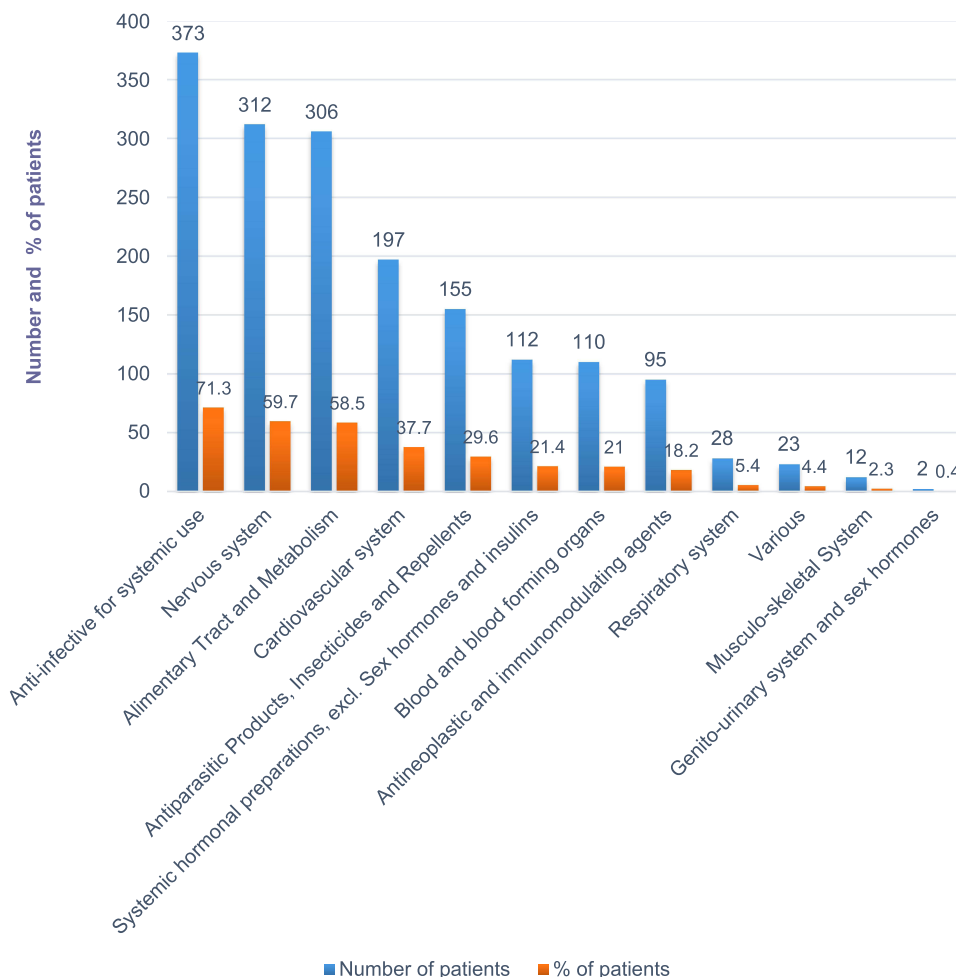
Figure 3 Medications used by older adults 60 years and above admitted at MRRH, Southwestern Uganda from November 2020 to May 2021.

trained staff, scarce training programs, indistinct roles, and poor coordination of activities as well as lack of capacity to monitor medicines and evaluate risks as well as under-reporting of ADRs.[23,60] Patient factors contributing to more ADR may include lack of access to safe and effective medicines as well as inability to afford the necessary laboratory tests done for monitoring of medication safety.

The current higher prevalence may also be explained by our prospective study design and our ADR identification method that involved daily patient interviews and physical examination to detect ADRs in addition to reviewing patient records. As discussed above, previous studies showed that prospective observational studies[18,61] and studies employing patient interviews in addition to reviewing patient records[62] detected more ADRs compared to retrospective studies and studies that solely depended on medical records. Moreover, being conducted in a referral hospital might have resulted in a higher prevalence of ADRs as compared to some of the previous

studies that were done in lower-level facilities. This may be related to a more severe and complex comorbidity as well as a wider range of available and prescribed medications including cancer chemotherapy.

On the other hand, the current prevalence is comparable with 46% from a study in Belgium[32] and lower than the prevalence of 64% from India.[34] The current prevalence is also comparable with the 49.5% prevalence of ADR among hospitalized general adults in Uganda.[40] However, our finding was higher than an incidence of 25% among adult inpatients in Mulago hospital.[41] The deviation is likely due to older adults having a higher risk of ADR because of physiologic changes resulting in pharmacokinetic variations of medicines that make them more susceptible to ADRs and often have more comorbidities and a higher number of concurrent medications.[6,8,9,29,63]

Similarly, the current incidence of 78 ADRs per 1000 person-days is higher than the incidence of 15.2 per 1000 person-years reported by a study in Canada[55] and

Adverse drug reactions
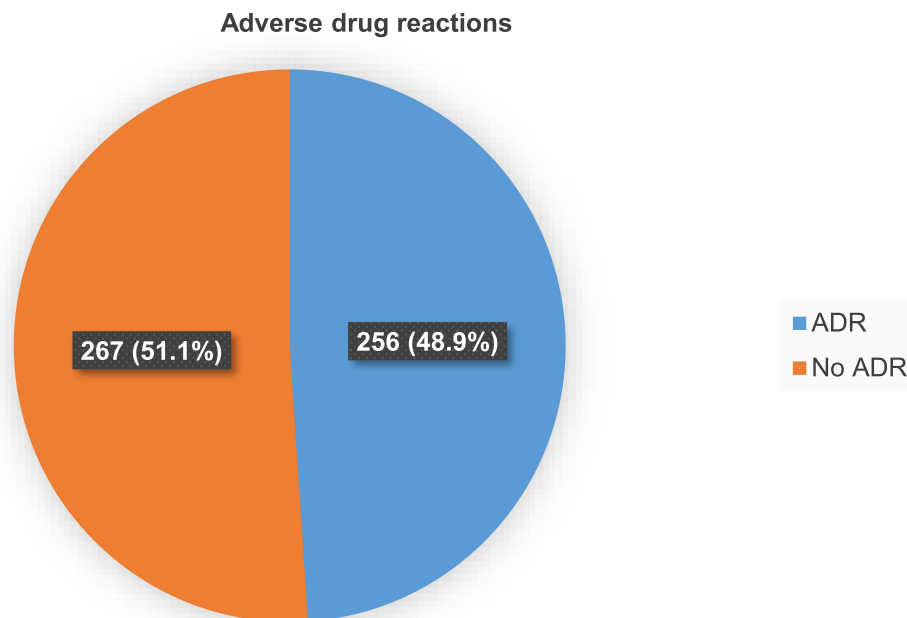

267 (51.1%)   256 (48.9%)

■ ADR
■ No ADR

Figure 4 The prevalence of adverse drug reactions among older adults 60 years and above admitted at MRRH, southwestern Uganda from November 2020 to May 2021.

the incidence of 0.23 ADRs/admission in England.[16] This difference is probably because Sikdar et al employed a retrospective study design and both Sikdar et al and Sari et al solely depended on the patient records, whereas our study was a prospective cohort and involved daily patient interviews and physical examination to detect ADRs in addition to reviewing patient records. Using medical record review and patient interviews detects considerably more ADRs than sole medical record review.[62] Previous systematic reviews revealed that prospective observational studies have a higher ADR detection rate than retrospective studies because in prospective studies, in addition to reviewing the medical records, participants are also interrogated and observed.[18,61]

Out of the 365 ADRs identified, most (260, 71.2%) were rated as probable, 101 (27.7%) as possible, and 4 (1.1%) as definite ADRs using the Naranjo ADR causality

Table 2 The Incidence of Adverse Drug Reactions Among Older Adults 60 Years and Above Admitted at MRRH, Southwestern Uganda from November 2020 to May 2021

S.No.	Parameter	Frequency
1	Total number of ADR incidents	365 ADRs
2	Total person-days	4702 person-days
3	ADRs/person-day×1000	78 ADRs/1000 person-days
4	ADRs/admission	0.7 ADRs/admission

scale. This result is comparable with several previous studies that revealed most of the ADRs reported among hospitalized older adults were probable including 76.5% in Australia,[15] 71% in Belgium,[32] 67% in Germany,[57] 66% in Ireland[29] and 62–72% in India.[28,59]

ADRs affecting the gastro-intestinal tract were the most frequently (40.6%) identified categories followed by ADRs involving the central nervous system (20.5%), endocrine and metabolic system (8.8%), and cardiovascular system (8.5%). These results are in line with findings of previous studies that had shown ADRs affecting endocrine and metabolic system,[9,25,29,30] gastrointestinal tract,[9,25,30,34,64] nervous system[9,29,30] and cardiovascular system[29,64] to be the top three most commonly encountered types among elderly inpatients. The most frequently detected specific ADRs were constipation,[42] nausea,[38] nausea and vomiting,[36] dizziness,[29] drowsiness,[16] hypotension,[16] and hypoglycemia.[13]

The largest proportion of ADRs affecting the gastro-intestinal tract was constipation (mostly associated with three nervous system agents: tramadol, morphine, and diclofenac) and nausea with or without vomiting, which was particularly associated with anti-infective/anti-parasitic and anti-neoplastic agents. Similarly, most of the ADRs affecting the nervous system were dizziness (mainly associated with anti-infective agents and cardio-vascular drugs) and drowsiness (mainly associated with nervous system agents).

Table 3 The Categories of ADRs Detected Among Older Adults 60 Years and Above Admitted at MRRH, Southwestern Uganda from November 2020 to May 2021

Category of ADR	Frequency (%)	Frequencies of Specific ADRs Detected (N=365)
Gastrointestinal	148 (40.6)	Constipation (42), Nausea (38), Nausea and vomiting (36), Abdominal pain (10), Anorexia (7), Dyspepsia (3), Flatulence (3), Gastric irritation (3), Stomatitis (2), Dysgeusia (2), Diarrhea (2)
Central nervous system	75 (20.5)	Dizziness (29), Drowsiness (16), Headache (10), Malaise (4), Vertigo (5), Insomnia (4), Confusion (2), CNS depression (1), Lethargy (1), CNS toxicity (1), Depression (1), Seizure (1)
Cardiovascular	32 (8.8)	Hypotension (16), Hypertension (5), Arrhythmia (5), Edema (4), Palpitation (1), Syncope (1)
Endocrine & metabolic	31 (8.5)	Hypoglycemia (13), Hyponatremia (4), Hyperglycemia (4), Hypokalemia (6), Hyperkalemia (2), Increased thirst (1), Hypernatremia (1)
Dermatologic	18 (4.9)	Diaphoresis (7), Skin rash (5), Pruritus (5), Urticaria (1)
Peripheral nervous system	11 (3.1)	Extrapyramidal reaction (4), Paresthesia (3), Peripheral neuropathy (2), Restlessness (1), Rigors (1)
Neuromuscular & skeletal	13 (3.6)	Asthenia (9), Muscle spasm (2), Fatigue (1), Back pain (1)
Otic	6 (1.6)	Tinnitus (3), Hearing loss (3)
Miscellaneous	6 (1.6)	Fever (6)
Local	6 (1.6)	Induration at the injection site (4), Skin tightness (2)
Hypersensitivity	5 (1.4)	Hypersensitivity reaction (4), Angioedema (1)
Renal	4 (1.1)	Renal failure (4)
Genitourinary	3 (0.8)	Vaginitis (1), Dysuria (1), Vaginal candidiasis (1)
Hematologic & oncologic	3 (0.8)	Bleeding (2), Leukopenia (1)
Respiratory	3 (0.8)	Bronchospasm (2), Cough (1)
Hepatic	1 (0.3)	Hepatitis (1)

Abbreviation: CNS, central nervous system.

On the contrary, a study in India,[34] as opposed to the current study and the majority of the literature, showed dermatologic system and the hematologic system as the most commonly affected by ADR next to the gastrointestinal tract. This deviation is probably because the former solely conducted the study among cancer patients and thus, dermatological ADRs like alopecia and hematologic ADRs like bone marrow suppression were highly prevalent because of the widespread use of chemotherapeutic agents by the participants.

Most (83.6%) of the ADRs were categorized as "Type A" followed by "Type B" (12.6%) and 'Type C (1.6%). The type C ADRs occurred during hospitalization were related to longer hospitalization of up to 34 days of the study patients. We also included ADRs like extrapyramidal reactions with antipsychotics and peripheral neuropathy with isoniazid, which occurred after hospitalization from a drug, which had been initiated before the current admission. The type F ADR that was identified in this study was treatment failure (hyperglycemia) related to dexamethasone for a patient whose fasting blood sugar was previously well controlled with insulin therapy.

The current percentage of type A ADRs is slightly lower compared to proportions of 92%[59] and 94%[27] type-A ADRs though both of these studies also used Rawlins and Thompson classification. This difference is likely because we employed the ABCDEF classification that added type C (dose and time dependent or chronic reactions), type D (delayed reactions), type E (withdrawal reactions), and type F (failure of therapy) types of ADRs to merely type A and B of Rawlins and Thompson classification,[50] which was used by the previous studies. This resulted in the categorization of some ADRs into type C(6) E(5) and F(3) which would have been, otherwise, fallen under the type A category.

Table 4 The Characteristics of the Detected ADRs Among Older Adults 60 Years and Above Admitted at MRRH, Southwestern Uganda from November 2020 to May 2021

Variables	Category	Frequency	Percentage (N=365)
Mechanism of ADR	Type A (Dose-dependent reactions)	305	83.6
	Type B (Bizarre reactions)	46	12.6
	Type C (Chronic reactions)	6	1.6
	Type E (Withdrawal reactions)	5	1.4
	Type F (Failure of therapy)	3	0.8
Severity of ADR	Mild	237	64.9
	Moderate	118	32.3
	Severe	10	2.8
Preventability of ADR			
Non-preventable		200	54.8
Definitely preventable	There was a previous ADR or allergy to the drug	47	43.9[a]
	The drug involved was inappropriate to the patient	39	36.5[a]
	Inappropriate dose, route or frequency given	21	19.6[a]
	Total	107	29.3
Probably preventable 58 (15.9%)	Monitoring tests were not performed	22	37.9[b]
	Drug interaction was involved in ADR	17	29.3[b]
	Preventive measures not given	19	32.8[b]
	Total	58	15.9

Notes: [a]The denominator is 107. [b]The denominator is 58.

On the other hand, the proportion of type B ADRs was slightly higher compared to 6% in the UK[27] and 8% in India[59] probably because of our higher study population, which may have resulted in the disproportionate increase of type B ADRs as these ADRs occur rarely and are often underestimated in smaller studies. This deviation might also be explained by the involvement of patients on cancer chemotherapy that consisted of combinations of several agents associated with hypersensitivity reactions. Moreover, we might have detected type B ADRs like mild hypersensitivity reactions, fever, and skin rashes more than previous studies because used patient interview as opposed to merely reviewing medical records for ADR identification.

Almost two-thirds (64.9%) of the ADRs were mild, whereas 32.3% and 2.8% were moderate and severe, respectively. The current proportion of severe ADRs is comparable with results from two studies from India that reported 0% and 1%; however, considerably lower than proportions from high-income countries (HICs) that ranged from 9% to 72%.[15,25,27,29,56,57] This difference may be related to having more complex comorbidity, advanced age, and more access to newer medications in HICs. A previous systematic review showed that the proportion

of severe ADRs was higher in HICs and in patients with greater comorbidity who take more medications.[61] The exclusion of patients who died or were transferred to ICU within 48 hours of admission, possibly associated with ADRs, might have reduced the proportion of severe ADRs. Likewise, delays and inconsistencies of diagnostic tools and laboratory tests in our setting might have concealed potential severe ADRs, including renal failure, hepatotoxicity, electrolyte imbalance, bleeding. Additionally, the differences between the methods used to grade the severity of the ADRs may have added to the differences.

Nearly half (45.2%) of the ADRs were preventable; 15.9% were probably preventable, whereas 29.3% were definitely preventable provided that active risk identification and intervention had been done by prescribers, pharmacists, or nurses. From the current findings, avoiding drugs that had previously caused an ADR, avoiding medications that are inappropriate to the patient, optimizing the dosage regimen, conducting the necessary monitoring tests regularly, and checking for significant drug interactions are the most important interventions to prevent ADRs. This result is comparable with 48% reported by a study in India.[59] However, this proportion of preventable

Table 5 The Drugs Implicated in the Identified ADRs and the Associated Specific ADRs Among Hospitalized Older Adults, MRRH, Uganda

ATC Classes of the Drugs Used (Frequency, %)	Specific Drugs (Associated ADRs) N=365 ADRs
C: Cardiovascular system drugs (76, 20.8)	**Furosemide** (n=38: Dizziness (5), Hyponatremia (5), Hypotension (5), Hypokalemia (4), Vertigo (4), Constipation (3), Muscle spasm (2), Asthenia (2), Hearing loss (2), Drowsiness (1), Restlessness (1), Gastric irritation (1), Nausea (1), Headache (1); Fever (1)); **Digoxin** (n=7: Arrhythmia (3), Dizziness (2), Asthenia (1), Abdominal pain (1)); **Spironolactone** (n=4: Nausea (2), Hyperkalemia (2)); Nifedipine (n=4: Dizziness (1), Headache (1), Asthenia (1), Constipation (1)); **Carvedilol** (n=3: Syncope (1), Hypotension (1), Fatigue (1)); **Enalapril** (n=3: Hypotension (2), Renal failure (1)); **Bisoprolol** (n=2: Arrhythmia (1), Hypotension (1)); **Methyldopa** (n=2: Flatulence (1), Hypertension (1)); ISD (n=2: Hypotension (2)); **Captopril** (n=2: Cough (1), Renal failure (1)); **Amlodipine** (n=1: Hypotension), **Atenolol** (n=1: Arrhythmia); **Atorvastatin** (n=1: Malaise); **Diltiazem** (n=1: Asthenia); **Losartan** (n=1: Hypotension); **Nifedipine and Losartan** (n=1: Hypotension); **Tolvaptan** (n=1: Increased thirst); **Digoxin and Furosemide** (n=1: Dizziness); **Hydrochlorothiazide** (n=1: Hyperglycemia)
N: Nervous system agents (75, 20.5)	**Tramadol** (n=38: Constipation (25), Diaphoresis (4), Nausea (2), Nausea and vomiting (2), Insomnia (2), Drowsiness (1), Tinnitus (1), Seizure (1)); **Morphine** (n=16: Constipation (7), Drowsiness (4), Dizziness (2), Hypotension (2), Insomnia (1)); **Diclofenac** (n=7: Dyspepsia (3), Constipation (2), Heart burn (1), Pruritus (1)); **Phenytoin** (n=5: Dizziness (1), Drowsiness (2), Edema (2)); **Chlorpromazine** (n=2: Extrapyramidal reaction (1), Constipation (1)); **Chlorpromazine and Haloperidol** (n=2: Extrapyramidal reaction (2)); **Haloperidol** (n=1: Lethargy); **Paracetamol** (n=1: Skin rash); **Risperidone** (n=1: Extrapyramidal reaction); **Pethidine** (n=1: Constipation); **Diazepam** (n=1: CNS depression)
J: Anti-infective for systemic use (71, 19.4)	**Ceftriaxone** (n=51: Dizziness (15), Nausea (14), Nausea and vomiting (5), Induration at injection site (3), Diaphoresis (2), Headache (2), Skin rash (2), Pruritus (2), Skin tightness (2), Dysgeusia (1), Fever (1), Drowsiness (1), Flatulence (1)); **Ciprofloxacin** (n=5: Nausea (3), Constipation (1), Bronchospasm (1)); **Dolutegravir** (n=3: Hyperglycemia (2), Depression (1)); **Isoniazid** (n=2: Peripheral neuropathy (1), Hepatitis (1)); **Fluconazole** (n=2: Nausea and vomiting (1), Abdominal pain (1)); **Clarithromycin** (n=1: Abdominal pain); Efavirenz (n=1: CNS toxicity); **Piperacillin and tazobactam** (n=1: Rigors); **Co-trimoxazole** (n=1: Abdominal pain); **Azithromycin** (n=1: Abdominal pain); **Clindamycin** (n=1: Pruritus); **Cloxacillin** (n=1: Urticaria); **Amoxicillin clavulanate** (n=1: Nausea)
L: Antineoplastic and immunomodulating agents (69, 18.9)	**Docetaxel** (n=12: Nausea and vomiting (7), Edema (2), Anorexia (2), Nausea (1)); **Capecitabine** (n=6: Anorexia (3), Paresthesia (2), Stomatitis (1)); **Cisplatin and Fluorouracil** (n=5: Nausea and vomiting (5)); **Doxorubicin** (n=5: Nausea and vomiting (3), Asthenia (2)); **Epirubicin and Cisplatin** (n=4: Nausea (1), Nausea and vomiting (3)); **Cisplatin** (n=4: Tinnitus (2), Nausea and vomiting (1), Renal failure (1)); **Fluorouracil** (n=4: Confusion (1), Anorexia (1), Nausea (1), Stomatitis (1)); **Rituximab** (n=3: Asthenia (2), Pruritus (1)); **Dacarbazine** (n=3: Nausea (1), Paresthesia (1), Anorexia (1)); **Paclitaxel** (n=3: Peripheral neuropathy (1), Nausea (1), Hypersensitivity reaction (1)); **Erlotinib** (n=2: Skin rash (2)); Goserelin (n=2: Headache (1), Diaphoresis (1)), **Epirubicin** (n=2: Hypersensitivity reaction (2)); **Vincristine and Rituximab** (n=2: Fever (2)); **Gemcitabine and Docetaxel** (n=2: Nausea and vomiting (1), Fever (1)); **Bicalutamide** (n=1: Back pain (1)); **Carboplatin** (n=1: Hearing loss); **Docetaxel and Carboplatin** (n=1: Nausea and vomiting); **Fluorouracil, Doxorubicin and Cyclophosphamide** (n=1: Nausea); **Gemcitabine and Carboplatin** (n=1: Nausea and vomiting); **Irinotecan** (n=1: Fever); **Oxaliplatin** (n=2: Nausea and vomiting (1), Leukopenia (1)); **Oxaliplatin and Capecitabine** (n=1: Nausea and vomiting); **Sorafenib** (n=1: Renal failure)

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Table 5 (Continued).

ATC Classes of the Drugs Used (Frequency, %)	Specific Drugs (Associated ADRs) N=365 ADRs
A: Alimentary Tract and Metabolism agents (25, 6.8)	**Insulin** (n=11: Hypoglycemia (11)); **Lactulose** (n=3: Nausea (1), Diarrhea (1), Flatulence (1)); **Metformin** (n=3: Diarrhea (1), Hypoglycemia (2)); **Ascorbic acid** (n=2: Headache (1), Nausea (1)); **Bisacodyl** (n=2: Abdominal pain (2)); **Metoclopramide** (n=3: Headache (1), Drowsiness (1), Bronchospasm (1)); **Lansoprazole** (n=1: Vomiting)
P: Antiparasitic Products, Insecticides and Repellents (23, 6.3)	**Metronidazole** (n=23: Drowsiness (5), Nausea (4), Headache (3), Nausea and vomiting (2), Confusion (1), Dysuria (1), Vaginitis (1), Vertigo (1), Candidiasis (1), Malaise (1), Dysgeusia (1) Dizziness (1), Insomnia (1))
H: Systemic hormonal preparations, excl. Sex hormones and insulins (10, 2.7)	**Dexamethasone** (n=5: Malaise (2), Hyperglycemia (1), Hypertension (1), Nausea (1)); **Hydrocortisone** (n=4: Angioedema (1), Hypernatremia (1), Hypertension (2)); **Prednisolone** (n=1: Hypertension)
B: Blood and blood forming organs (9, 2.7)	**Ferrous sulfate** (n=3: Nausea (2), Abdominal pain (1)); **Warfarin** (n=2: Bleeding (2)); **Potassium chloride** (n=2: Gastric irritation (1), Abdominal pain); **FeFol** (n=1: Abdominal pain); **Enoxaparin** (n=1: Injection site induration)
R: Respiratory system agents (4, 1.1)	**Bromhexine** (n=1: Gastric irritation); **Chlorpheniramine** (n=1: Drowsiness); **Cyproheptadine** (n=1: Hypersensitivity reaction); **Salbutamol** (n=1: Palpitation)
V: Various (2, 0.5)	**Kayexalate** (n=2: Constipation (1), Vomiting (1))
G: Genito-urinary (1, 0.3) system and sex hormones	**Sildenafil** (n=1: Dizziness)

Notes: Bold: Drugs implicated in the ADRs listed.
Abbreviations: CNS, central nervous system; ISD, isosorbide dinitrate; FeFol, ferrous sulfate and folic acid.

ADRs is lower compared to proportions ranging from 63% to 80% in studies of HICs.[15,27,32,57] This is probably because the proportion of severe ADRs was higher in those studies and it had been established that severe ADRs are more preventable than mild ADRs.[65]

Cardiovascular drugs (20.8%) and drugs acting on the nervous system (84% of which were analgesics) (20.5%) were shown to be the most common causes of ADRs. Constipation attributed to tramadol,[25] electrolyte disorders related to furosemide,[14] and hypotension associated with antihypertensives[10] were the most notable ADRs among others. These two classes were the fourth (used by 197 patients) and the second (used by 312 patients) most commonly used, respectively.

These findings are comparable with several previous studies that reported cardiovascular agents,[9,14,25–32] drugs acting on the nervous system (particularly NSAIDs, opioids, anticonvulsants, and antipsychotics),[9,14,27,29,31–33] anti-infective agents[25–27,30,33] and antineoplastic agents[31,33,34] as among the top three classes of drugs most frequently implicated in ADRs among hospitalized older patients.

From the descriptive statistics, a relationship was observed between how frequently each class of drug was used and how much of the ADRs were attributed to the respective class except for cardiovascular agents and antineoplastic drugs that were implicated in a disproportionally higher proportion of ADRs based on their frequency of use. This is probably because older patients are more susceptible to the ADRs commonly associated with these classes of medications like CNS side effects, renal toxicity, hypotension, electrolyte disturbances, and bone marrow suppression. With aging, physiological change and renal impairment lead to altered pharmacokinetic and pharmacodynamic changes of drugs and making the older adults highly susceptible to adverse drug reactions.[6]

On the other hand, the proportion of ADRs related antithrombotic agents (2.7%) is considerably lower in our study compared to the previous studies.[9,14,25,28,32] This can be explained by a limitation of delays and inconsistencies in the use of coagulation tests to monitor for the ADR of these agents in our setting. This problem was observed to be widespread and was attributed to the unavailability of the tests as well as the inability of patients to afford to pay the fee out of pocket.

The strengths of the current study include being prospective design, random sampling technique, and having team of experts that comprised of senior clinical

pharmacists and physicians. On the other hand, the study had some limitations. First, the unavailability of some essential laboratory or diagnostic tests that might result in missing certain types of ADRs. Secondly, being conducted at a regional referral hospital might reduce the generalizability of the results in lower-level health facilities where some classes of drugs or specific agents that have been implicated in the currently reported ADRs are not available. Thus, we recommend the future study to include different levels of facilities, be multi-centered, and be conducted for a longer period. These findings should, therefore, be carefully interpreted as the study is a single centered and conducted only for a period of 6 months.

Studies focusing on predictors of ADRs are crucial to develop preventive strategies which help to mitigate the burden of ADRs.[66,67] However, such studies are scarce in low- and middle-income countries.[61] These findings therefore provide a basis for future studies to develop, adapt and test context-relevant ADRs prediction models to improve patient safety and the medicine experience among the increasing elderly population in Uganda and other low- and middle-income countries.

Conclusion

Half of hospitalized older patients experienced at least one ADR during their hospital stay, whereas nearly one in ten experienced an ADR per day during hospitalization. The current ADR prevalence and incidence are considerably higher compared to results from high-income countries and slightly higher than those from middle-income countries. Almost three-thirds of the ADRs were rated as probable. ADRs affecting gastro-intestinal tract, central nervous system, endocrine and metabolic system, and cardiovascular system were the top-four most frequently identified categories. About 4 out of 5 of the ADRs were type A, whereas almost two-thirds were mild. Nearly half of the ADRs were preventable. Responsible for about one-fifth of all ADRs each, cardiovascular drugs and drugs acting on the nervous system were drug classes most frequently implicated in ADRs. Studies to develop and test context-relevant ADR prediction models among the elderly populations are thus warranted.

Abbreviations

ADR, Adverse Drug Reaction; ART, Anti-Retroviral Therapy; ATC, Anatomical Therapeutic; BNP, British National Formulary; BUN, Blood Urea Nitrogen; CCI, Charlson Comorbidity Index; CI, Confidence Interval; DDI, Drug–Drug Interaction; eGFR, Estimated Glomerular Filtration Rate; ICD, International Statistical Classification of Diseases; MRRH, Mbarara Regional Referral Hospital; MUST, Mbarara University of Science and Technology; REC, Research Ethics Committee; NSAID, Non-Steroidal Anti-Inflammatory Drugs; PIM, Potentially Inappropriate Medications; SPSS, Statistical Package for the Social Science; TB, Tuberculosis; UK, United Kingdom; UNCST, Uganda National Council for Science and Technology; US, United States of America; WHO, World Health Organization.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki (54). The study protocol was approved by the Research and Ethics Committee (REC) of MUST (Letter reference: MUREC 1/7-2020) and registered by UNCST. Then we obtained clearance from MRRH and informed consent from each participant.

Consent for Publication

All authors agreed to the submission of this manuscript for publication in addition to the consent to publish which was included in the informed consent form which attained ethical and participant approval.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design,

execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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