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Prevalence and Its Predictors of Drug-Related Hospitalizations among Patients Visited Emergency Departments of Addis Ababa City Hospitals in Ethiopia: A Multicenter Prospective Observational Study

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ABSTRACT

Objectives: The aim of this study was to determine the prevalence, categories and its predictors of drug related hospitalizations (DRHs) among patients visited at emergency departments of Addis Ababa city hospitals in Ethiopia.

Design: A multicenter prospective observational study was conducted through patients interview and review their medical chart.

Settings: The study was undertaken in three tertiary care hospitals, Addis Ababa, Ethiopia.

Participants: A total of 423 patients who fulfilled the inclusion criteria were recruited.

Outcome measures Prevalence and preventability of drug related hospitalizations, categories of drug related problems causing drug related hospitalizations, medications and diseases involved in drug related hospitalizations and factors independently associated with them.

Result: 423 participants who fulfilled the inclusion criteria were enrolled in the study. Of those, more than half of them (216, 51.1%) were females. The mean age (SD) of the study participants was 47.50 (±17.21) years. The mean length of hospital stay (SD) was 10.29(±8.99) days. Among the included participants, near to three-fifth (245, 57.9%) of patients were hospitalized due to drug related problems, of which 87.8% were preventable. Of those, more than half (130, 53%) of them were noted from failure to receive drugs followed by untreated indications (94, 37.8%). Factors associated with DRHs were age ≥ 65 years (Adjusted Odds Ratio [AOR]=7.451,95%CI: 1.889-

29.397), tertiary educational level (AOR=0.360, 95%CI: 0.141-0.923), participants who did not have any occupation (AOR=3.409, 95%CI: 1.120-10.374), presence of co-morbid conditions (AOR=2.004, 95%CI: 1.095-3.668), and hospital stay > 7 days (AOR=2.186, 95%CI: 1.412-3.382).

Conclusion: Nearly 90% of DRHs were deemed to be preventable in the study settings. Older age, lower educational level, unemployment, presence of co-morbid condition and staying > 7 days in hospital as an inpatient were predictors of DRHs.

Strength and limitations of the study

- As to our knowledge, this study is the first study in Africa continent.
- The strength of this study is the study design that is a prospective observational study which is specifically tailored to evaluate direct impact of drug related problems on treatment or preventive measures on disease. This study was a multicenter, therefore, representativeness of the finding is more accepted and convinced.
- And also, the sample size was sufficiently large to estimate the incidence and predictors of DRHs.
- One of the main limitations of this study was there are no standardized procedures for immediate recording and reporting DRHs which may result in to limit the real estimation of the prevalence of DRHs. This problem was mitigated by using clinical pharmacists who have an ability to identify and resolve drug related problems at emergency department.
- A factor limiting the scope of this study concerned patients admitted to an emergency ward. Hence, considerable numbers of patients with DRPs from other major departments have been missed.

INTRODUCTION

Though drugs can be ordered for the intention of achieving desired health outcomes that improve the patient's quality of life, any symptom and sign of the disease causing drug related hospitalizations (DRHs) as a result of drug related problems (DRPs) can be appeared.[1-3] DRP was defined according to Helper and strand as 'an undesired event or circumstance due to drug therapy that actually or potentially interferes with desired health outcomes'.[4]

In the globe, medications use has been becoming increased because of the presence of large numbers of diseases which in turn contributed to the production of medications in advances from pharmaceutical industries. Therefore, advances in drug therapies led to an apparent increase in the incidence of DRPs leading hospitalization. Hospitalization can be defined as drug related if it is straightforwardly linked to one of eight predefined Helper's and Strand's classifications of DRPs: adverse drug reaction (ADR), drug interaction, improper drug selection, untreated indication, sub-therapeutic dosage, supra-therapeutic dosage, failure to receive drugs, and drug use without indication.[5-11] Those DRPs can arise when a medicine is prescribed aptly and used correctly (e.g., ADR), due to errors involving prescribing (including inappropriate or over-treatment, and failure to prescribe the indicated treatment or under-treatment), dispensing, administering, reconciling, or monitoring of medicines and from patient poor adherence.[2 12 13] According to the World Health Organization (WHO), an ADR is any harmful, undesired and inadvertent drug effect that occurs at doses used in human for therapy, diagnosis or prophylaxis.[14]

Over the past decades, DRHs have been stated as prevailing. In the United States, 17 million emergency department (ED) visits and 8.7 million hospital admissions accounted from DRPs annually.[15] It increases morbidity and mortality rates, health care cost, decreases income and household productivity and reduced quality of life.[2 16 17]

The studies carried out in different study areas of the globe manifested the extent of DRHs have been estimated to be between 16% to 41.3%. Of those, 50% to 95% were preventable. Among DRHs; supratherapeutic dosage (10.3%-12.7%), non-compliance (10.6%-65.8%), ADRs (10.7%-45.5%) and untreated indications (10.7-13.3% were frequently identified. [5 8 16 18-20]

DRPs resulting DRHs were defined as preventable if the patient failed to take a drug that is known to reduce or prevent the symptoms according to the prescribed directions, took a drug for which a patient had a known allergy, drug treatment was obviously improper, dosage differed from accepted recommendations, took a drug that was not indicated, and if there was a failure to monitor by a physician at reasonable time intervals and inadequate monitoring due to inability to see a physician e.g., financial difficulties whilst if there was no reasonable actions to prevent DRPs which is termed as non-preventable. [18 21]

In many studies, patients with DRHs had mainly cardiovascular diseases and diabetes. In those diseases, cardiovascular drugs and hypoglycemic medications were involved in DRHs. [5 9 10 16 18 19 22 23] Studies previously investigated that polypharmacy, advanced age and comorbid conditions were factors that favor the occurrence of DRHs. [3 5 18 19]

It is important to determine DRHs prevalence to improve treatment outcomes and prevent unnecessary preventable admissions. So, to the best of our knowledge there are no studies about DRHs in Ethiopia. Therefore, the present study aimed to determine the prevalence, categories and its predictors of DRHs among patients admitted to an emergency ward (EW) of the three selected hospitals in Addis Ababa City, Ethiopia.

METHODS

Study Settings

The study was carried out in EW of Tikur Anbessa Specialized Hospital (TASH), Zewditu Memorial Hospital (ZMH) and Yekatit 12 Hospital Medical College (Y12HMC), Addis Ababa city, Ethiopia. TASH was inaugurated in 1972. It has 700 beds and it is a tertiary care teaching hospital of Addis Ababa University. In TASH, outpatient, inpatient and emergency services are delivered. The ED provided services to about 13,920 patients per year. Y12HMC was established in 1923. It is also a tertiary carry level referral and teaching hospital in Addis Ababa that provides both inpatient and outpatient treatment for a large number of people from the Addis Ababa city and different nation parts. The hospital has total of three ED rooms. The adult medical ED is collocated with adult surgical ED. It served around 10,560 patients per year in ED. The third hospital where in this study was carried out is ZMH which was built and owned by the Seventh day Adventist Church, but was nationalized during the Derg regime in 1976 and it is one of a teaching and general referral hospitals in Ethiopia and it served for about 10,560 patients per year at ED.

Patient involvement

Patients did not participate in the initial conception and design of the study. However, based on the comments of the pretest (5% of the sample size) participating patients, we have made a correction on the patient approach and timing for an interview during data collection. Patients played the central role in this study in determining the level of medication use, adherence and medical history.

Study design and population

A prospective observational study design was used and the data were collected from August to September, 2020 using a structured questionnaire which was developed from related articles that were rigorously evaluated. All patients who admitted at EW of the three selected hospitals during the study period and those who fulfilled the inclusion criteria were recruited.

Inclusion and exclusion criteria

Patients who had medical history with completed data and patients greater than and equal to 14 years old were included. Whereas, Patients who had incomplete or no medical records, patients who were refuse to participate, patients presented with trauma and injuries associated with accidents (e.g. road traffic accidents, beaten by stick, stabbing and bulleting) and who were poisoned/intoxicated (for instance snake bite, alcohol intoxication or use of pesticide) were excluded.

Sample size determination and techniques

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

$n = [(Z\ \alpha/2)^2 \times p\ (1-p)] \vee d^2 = [(1.96)^2 \times 0.5x0.5] / 0.05^2 = 384$

(Hence; n = required sample size, Z α/2 = critical value for normal distribution at 95% confidence interval which equals 1.96 (*Z* value at alpha = 0.05), P = Proportion of drug related hospitalization =0.5, d = margin of error of 5%=0.05. The calculated sample size using this formula was 384. Adding 10% contingency (for non-response rate), it makes the final sample size to be 423. Therefore, this research was being conducted in three hospitals, 169 participants were included from TASH, 127 participants from ZMH and other 127 participants from Y12MHC.This was

computed according to the three hospitals patients per year services proportion in EW as it is mentioned in the section of study settings.

Data collection procedures

Structured data collection tools were used by three pharmacists to obtain the necessary data including the patient's demographic details and clinical information related to numbers of medications being taken prior to admission by interviewing the patients. Furthermore, patient's medical records were reviewed by data collectors to identify clinical information (disease history, allergic status, admission diagnosis, length of hospital stay during admission, number of medications being taken prior to admission, data on laboratory investigations) and supplementary information and clarifications on some patient's medical information were obtained through discussion with the residents and interns. By applying those data gathering approach, different categories of DRPs resulting hospitalization with their possible independent associated factors were determined. Data collectors who were three pharmacists who had basic knowledge on pharmaceutical care services and also received training on how to collect data from patient's medication charts and on how to approach the patients and health care professionals and ways of using updated references such as Medscape, UpToDate, 2018 and Micromedex in order to determine the presence of DRPs brought DRHs. Once DRPs resulting DRHs were identified, they were recorded and classified using DRPs registration format according to Helper's and Strand's classification.

Data collection management

Pretest was performed on 5% patients in TASH prior to the actual data collection period and amendment was made accordingly. The data collection process was supervised, and data abstraction formats were reviewed and cheeked for their completeness every day to ensure its quality. Urgent correction was made, if any errors were identified.

Data analysis

The data were entered and analyzed using Statistical Package for Social Science (SPSS) version 26. Mean and standard deviation for continuous variables and frequency and percentage for categorical variables were computed by using descriptive statistics in SPSS to summarize socio-demographic and relevant clinical characteristics of the study participants. Tables and charts were used to present the results. Furthermore, univariate and multiple binary logistic regressions were performed to analyze factors that predict drug related hospitalizations; and variables whose p-values < 0.2 in the univariate analysis were included in the multiple binary logistic regressions to control the effect of confounders. The level of significance was chosen at p–value ≤ 0.05 and results were reported as odds ratios (OR) with 95% confidence intervals.

RESULTS

Socio-demographic and clinical characteristics of the study participants

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

As socio-demographic and clinical characteristics of the participants depicted in

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

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Gender			
Male	119(48.6)	88(49.4)	207(48.9)
Female	126(51.4)	90(50.6)	216(51.1)
Age (in years)			
Mean± SD	48.23±17.85		
14 - 24	24(9.8)	14(7.9)	38(8.98)
25- 39	51(20.8)	59(33.1)	110(26)

40 - 64	100(40.8)	74(41.6)	174(41.1)
>64	70(28.6)	31(17.4)	101(23.9)
Marital status			
Single	64(26.1)	34(19.1)	98(23.2)
Married	129(48.6)	105(59)	234(55.3)
widowed	20(8.2)	9(5.1)	29(6.7)
Divorced	42(17.1)	31(16.9)	73(17.3)
Education level			
No formal education	116(47.3)	72(40.4)	188(44.4)
Elementary	66(26.9)	47(26.4)	113(26.7)
Secondary	31(12.7)	35(19.7)	66(15.6)
Tertiary	32(13.1)	24(13.5)	56(13.2)
Residence			
Addis Ababa	177(72.2)	127(71.3)	304(71.9)
Out of Addis Ababa	68(27.8)	51(28.7)	119(28.1)
Religion			
Orthodox	186(76)	136(76)	322(76.1)
Muslim	42(17.1)	31(17.4)	73(17.3)
Catholic	1(0.4)	1(0.6)	2(0.5)
Protestant	16(6.5)	10(6)	26(6.1)

DRHs, drug related hospitalizations; non-DRHs, non-drug related hospitalizations; SD, standard deviation

Table 1 … Continued

Table 1 …. continued

Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Employment			
Employed	25(10.2)	25(14)	50(11.8)
Unemployed	0.0	1(0.6)	1(0.24)
House wife	30(12.2)	33(18.5)	63(14.9)
Merchant	13(5.3)	14(7.9)	27(6.4)
Student	18(7.3)	7(3.9)	25(5.9)
Laborer	51(20.8)	32(18)	83(19.6)
Retired	57(23.3)	40(22.5)	97(22.9)
Others	29(11.8)	14(7.9)	43(10.2)
Farmer	22(9)	12(6.7)	34(8)

Social habit (smoking cigarette)			
Yes	29(11.8)	15(8.4)	44(10.4)
No	216(88.2)	163(91.6)	379(89.6)
Social habit (dining alcohol)			
Yes	71(29)	57(32)	128(30.3)
No	174(71)	121(68)	295(69.7)
Physical activity(walk)			
Yes	165(39)	127(71.3)	292(69)
No	80(32.7)	51(28.7)	131(31)
Physical activity (regular physical exercise)			
Yes	5(2)	5(2.8)	10(2.4)
No	240(98)	173(97.2)	413(97.6)

[2] Others: participants who did not have any occupation rather they were dependent to live with other people.

DRH, drug related hospitalization; Non-DRH, Non-drug related hospitalization; n, number; SD, standard deviation

Table 1 …. continued

Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Other Drugs (including OTC, herbals)			
Yes	3(1.2)	0(0)	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Number of medications taken per patient			
Mean± SD	3.39±2.35		
0	24(9.8)	12(6.7)	36(8.5)
1	41(16.7)	26(14.6)	67(15.8)
2	35(14.3)	40(22.5)	75(17.7)
3-5	98(40)	75(42.1)	173(40.9)
>5	47(19.2)	25(14)	72(17)
Polypharmacy			
Yes	84(34.3)	43(24.2)	127(30)
No	161(65.7)	135(75.8)	296(70)
Co morbid condition			
Yes	137(55.9)	76(42.7)	213(50.4)
No	108(44.1)	102(57.3)	210(49.6)

Co morbid condition (Hypertension)			
Yes	68(27.8)	40(22.5)	108(25.5)
Co morbid condition (Diabetes mellitus)			
Yes	31(12.7)	22(12.4)	53(12.5)
Co morbid condition (Cardiac diseases)			
38(15.5)	21(11.8)	59(13.9)	
Length of Hospital stay (Days)			
1—7	101(41.2)	112(62.9)	213(50.4)
>7	144(58.8)	66(37.1)	210(49.6)
Mean± SD	11.4±9.27		
Median	9		
Range	2-96		

, more than half of the participants (216, 51.1%) were females. The mean (SD) age of the participants was 47.5 (±17.21) years and nearly two third (275, 65%) of the patients were age ≥ to 40 years. More than 70 % (301, 71.1%) of the total participants' level of education was below secondary school. Nearly three fourth of them (304, 71.9%) resided in Addis Ababa city. Out of the total study participants, (245, 57.9%) of them were taking ≥ three drugs prior to admission and (127, 30%) of the participants were taking ≥ five drugs which is termed as polypharmacy. Above half of the participants (213, 50.4%) had co-morbid diseases which have been hypertension (108, 22.5%), cardiac diseases (59, 13.5%) and diabetes mellitus (53, 12.5%) were predominant. The total length of hospital stay was 4352 days with a mean (SD) of 10.28±8.99 days and ranges from 2 to 96 days.

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

Variables	**[1]DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Gender			
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Female	126(51.4)	90(50.6)	216(51.1)

Age (in years)			
Mean± SD	48.23±17.85		
14 - 24	24(9.8)	14(7.9)	38(8.98)
25- 39	51(20.8)	59(33.1)	110(26)
40 - 64	100(40.8)	74(41.6)	174(41.1)
>64	70(28.6)	31(17.4)	101(23.9)
Marital status			
Single	64(26.1)	34(19.1)	98(23.2)
Married	129(48.6)	105(59)	234(55.3)
widowed	20(8.2)	9(5.1)	29(6.7)
Divorced	42(17.1)	31(16.9)	73(17.3)
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Muslim	42(17.1)	31(17.4)	73(17.3)
Catholic	1(0.4)	1(0.6)	2(0.5)
Protestant	16(6.5)	10(6)	26(6.1)

DRHs, drug related hospitalizations; non-DRHs, non-drug related hospitalizations; SD, standard deviation

Table 1 … Continued

Table 1 …. continued

Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Employment			
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Unemployed	0.0	1(0.6)	1(0.24)
House wife	30(12.2)	33(18.5)	63(14.9)
Merchant	13(5.3)	14(7.9)	27(6.4)
Student	18(7.3)	7(3.9)	25(5.9)
Laborer	51(20.8)	32(18)	83(19.6)

Retired	57(23.3)	40(22.5)	97(22.9)
Others[2]	29(11.8)	14(7.9)	43(10.2)
Farmer	22(9)	12(6.7)	34(8)
Social habit (smoking cigarette)			
Yes	29(11.8)	15(8.4)	44(10.4)
No	216(88.2)	163(91.6)	379(89.6)
Social habit (dining alcohol)			
Yes	71(29)	57(32)	128(30.3)
No	174(71)	121(68)	295(69.7)
Physical activity(walk)			
Yes	165(39)	127(71.3)	292(69)
No	80(32.7)	51(28.7)	131(31)
Physical activity (regular physical exercise)			
Yes	5(2)	5(2.8)	10(2.4)
No	240(98)	173(97.2)	413(97.6)

[2] Others: participants who did not have any occupation rather they were dependent to live with other people.

DRH, drug related hospitalization; Non-DRH, Non-drug related hospitalization; n, number; SD, standard deviation

Table 1 …. continued

Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Other Drugs (including OTC, herbals)			
Yes	3(1.2)	0(0)	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Number of medications taken per patient			
Mean± SD	3.39±2.35		
0	24(9.8)	12(6.7)	36(8.5)
1	41(16.7)	26(14.6)	67(15.8)
2	35(14.3)	40(22.5)	75(17.7)
3-5	98(40)	75(42.1)	173(40.9)
>5	47(19.2)	25(14)	72(17)

Table 1 …. continued

Polypharmacy			
Yes	84(34.3)	43(24.2)	127(30)
No	161(65.7)	135(75.8)	296(70)
Co morbid condition			
Yes	137(55.9)	76(42.7)	213(50.4)
No	108(44.1)	102(57.3)	210(49.6)
Co morbid condition (Hypertension)			
Yes	68(27.8)	40(22.5)	108(25.5)
Co morbid condition (Diabetes mellitus)			
Yes	31(12.7)	22(12.4)	53(12.5)
Co morbid condition (Cardiac diseases[3])			
38(15.5)	21(11.8)	59(13.9)	
Length of Hospital stay (Days)			
1–7	101(41.2)	112(62.9)	213(50.4)
>7	144(58.8)	66(37.1)	210(49.6)
Mean± SD	11.4±9.27		
Median	9		
Range	2-96		

Prevalence and categories of drug related hospitalizations

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

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

Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Untreated indications		94(38.5)
	Untreated medical condition is existed	34(36.2)
	Synergistic/ potentiating drug needed	42(44.7)
	Preventive/ prophylactic drug needed	18(19%)
Improper Drug Selection		16(6.5)
	More effective alternative drug is available	6(37.5)
	Condition is already refractory to drug	2(12.5)
	The drug is not effective for condition	6(37.5)
	Others[4]	2(12.5)

[4] Others; patients who were using expired drugs like insulin and albuterol.

Table 2 Continued……

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Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Sub therapeutic Dosage		30(12.2)
	Wrong dose (too small) of the drug	24(80)
	Frequency is inappropriate (long)	5(16.7)
	Duration of drug use is too short	1(3.3)
Supra therapeutic Dosage		13(5.3)
	Wrong dose (too high) of the drug	11(84.6)
	Frequency is inappropriate (short)	2(15.4)
Adverse drug reaction		38(15.5)
	Undesired effect from the drug is found	34(89.5)
	Unsafe drug for patient is existed	1(2.6)
	Dosage is administered too rapidly	1(2.6)
	Allergic reactions is found/reported	2(5.3)
Drug Interactions		1(0.4)
	There is (are) major drug interaction	1(100)

[5]Others; patients who were using expired drugs like insulin and albuterol.

Table 2 Continued…..

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Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Failure to receive drugs.		130(53.5)
	Does not understand instructions	6(4.6)
	Patients prefer not to take	43(33.1)
	Patients forget to take	3(2.3)
	Drug product not available	17(13.1)
	Cost of medication too expensive	16(12.3)
	Disbelieves on the drug effectiveness	1(0.8)
	Patients felt better	17(13.1)
	Patients felt worse	1(0.8)
	Fear of adverse events	18(13.8)
	Failure to follow-up due to Covid-19	8(6.2)
Total number of DRPs leading DRHs		322
Total number of participants with DRHs		245
Average number DRPs per patients with DRHs		1.31
Preventability of DRHs		215(87.8)

Medications and diseases involved in drug related hospitalizations

From the total 245 drug related hospitalized patients, nearly one third of them had the cardiovascular diseases (80,32.6%),of which heart failure accounted for (59, 24%) followed by endocrine disease(47,19.2%) with the prominent disease of diabetes mellitus(44,18%) and cerebrovascular disease which was stroke(26,10.6%).Patients who had HIV(15, 6.1%) and asthma (14, 5.7%) also accounted for more than 10% of DRHs as presented in Table 3 .

Table 3: Diseases that associated with drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

Disease's categories(n)	Name of specific disease	n,(%)
Cardiovascular diseases (n=80, 32.6%)	PAD	6(2.4)
	Hypertension	9(3.7)
	Heart failure	**59(24)**
	DVT	5(2)
	Ischemic heart disease	1(0.4)
	Schizophrenia	2(0.8)
CNS diseases (n=**8, 3.2%)**	Epilepsy	6(2.4)
Cerebrovascular disease (n=**26, 10.6%)**	**Stroke**	**26(10.6)**
Infectious diseases (n=**21, 8.5%)**	Tuberculosis	6(2.4)
	HIV	**15(6.1)**
Endocrine system diseases (n=47, 19.2%)	Thyroid storm	1(0.4)
	Diabetes mellitus	**44(18)**
	Hypoglycemia	2(0.8)

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

Table 3 Continued …….

Table 3 Continued…….

Disease's categories(n)	**Name of specific disease**	**n,(%)**
Diseases of cancer (n=**25, 10.1%)**	Colonic Cancer	2(0.8)
	Hematological malignancy	2(0.8)
	Melanoma	1(0.4)
	AML	3(1.2)
	NHL	3(1.2)
	Gastric Cancer	1(0.4)
	Lung cancer	2(0.8)
	MDS	1(0.4)
	HL	1(0.4)
	CLL	1(0.4)
	Hair cell leukemia	1(0.4)
	Breast cancer	3(1.2)
	Cervical cancer	2(0.8)
	[5]ALL	1(0.4)
	Myelofibrosis	1(0.4)
Diseases of the respiratory system (n=**21, 8.5%)**	COPD	3(1.2)
	Bronchoectiasis	3(1.2)
	Asthma	**14(5.7)**
	Corpulmonal	1(0.4)
GI diseases (n=**10, 4%)**	Dyspepsia	5(2)
	CLD	5(2)
	TEN	1(0.4)
Others (n=**7, 2.8%)**	Anemia	2(0.8)
	CKD	2(0.8)
	SLE and hemophilia	1 for each (0.8)

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

Total	245(100)

A total of 497 numbers of drugs were pertained to 245 patients DRHs. This entails that 2.03 drugs per patient were involved in DRHs. Of these, cardiovascular, chemotherapeutic and endocrine drug classes were the most frequently involved drugs which contributed to hospital admissions. Among cardiovascular drugs; furosemide (59,24.1%), angiotensin converting enzyme inhibitors (ACEIs) (48,19.1%), and antiplatelets and anticoagulants (44,18%) were most frequently mentioned followed by drugs act on the endocrine system; oral hypoglycemic agents (37, 15.1%) and insulin (24, 9.8%). And also, the chemotherapeutic drugs such as antibiotics (25 ,10%), anticancer drugs (23 ,9%), and combination antiretroviral therapy (15, 6.1%) were associated to the patients for DRHs. Medication classes and specific drugs reported in DRHs depicted in Table 4.

Table 4: Medication classes and specific drugs implicated in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

Drugs class	**Specific drugs**	**n (%)**
Cardiovascular drugs		
	Atorvastatin	31(12.7)
	Antiplatelets (aspirin,clopidogril)	24(9.8)
	Furosemide	59(24.1)
	Spironolactone	33(13.5)
	Anticoagulants (Warfarin, heparin)	20(8.2)
	Beta blockers (metoprolol,atenolol)	21(8.6)
	Digoxin	15(6.1)
	Angiotensin converting enzyme inhibitors (enalapril/lisinopril)	48(19.6)
	Calcium channel blockers (nifedipine, amlodipine)	34(13.9)
	Hydrochlorothiazide	11(4.5)

Table 4 Continued……..

Table 4 continued…..

Drugs class	**Specific drugs**	**n (%)**
Drugs act on the respiratory system		
	Long-acting beta blockers	15(6.1)
	bronchodilator	10(4.1)
Central nervous system drugs		
	Antiepileptics	5(2)
	antipsychotic	5(2)
	Amitriptylin	2(0.8)
Chemotherapeutic drugs		
	Antibiotics (piperacillin/tazobactam, meropenem, amoxicillin, amoxicillin/clavunic acid, ceftriaxone, benzathine penicillin)	25(10.2)
	Combination antiretroviral therapy	15(6.1)
	Anti-tuberculosis	13(5.3)
	Anticancer drugs	23(9.4)
Immuno-suppressants		
	Mycophenolate	1(.4)
	corticosteroids (prednisolone,budesonide)	9(3.7)
Endocrine drugs		
	Oral hypoglycemic drugs(metformin,glibenclamide)	37(15.1)
	Insulin	24(9.8)
	Propylthiouracil	4(1.6)
Gastrointestinal drug	Proton pump inhibitors	7(2.9)
Others	Potassium chloride	1(0.4)
	Non-steroidal anti-inflammatory drugs	3(1.2)

Opioid	1(0.4)

Table 4 Continued…….

Table 4 **Continued**

Drugs class	**Specific drugs**	**n (%)**
Others		
	Ferrous sulphate	1(0.4)
Total number of medications involved in DRHs		497
Total number of participants with DRHs		245(57.9)
Average number medications per patients with DRHs		2.03

Factors associated with the occurrence of drug related hospitalizations

According to the multivariate logistic regression analysis, five variables such as age, employment, presence of co morbid disease, length of hospital stay and education level were significantly associated with the occurrence of DRHs (See in Table 5). Age > 64 years (Adjusted Odds Ratio (AOR) =7.451, 95%CI: 1.889-29.397, P=0.004) which indicated that an increased age would make to develop DRHs. Tertiary educational level (AOR=0.360, 95%CI: 0.141-0.923, P=0.033) which indicates that being literate protect the participants from DRHs by 64% as compared to participants who had no formal education.

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

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

Table 5: Predictors that involved in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

	Causes of Patients hospitalization			**Odds Ratios**		
	[6]DRH (245)	**Non-DRH (178)**	**Total (423)**	**COR (95% CI)**	**AOR(95% CI)**	**P-value**
Variables	**n (%)**	**n (%)**	**n (%)**			
Age (Years)						
Mean ±SD	48.24±17.86		47.50±17.21			
14 - 24	24(9.8)	14(7.9)	38(8.98)	1.000	1.000	0.006
25- 39	51(20.8)	59(33.1)	110(26)	0.759(0.35-1.66)	1.55(0.51-4.66)	0.435
40 - 64	100(40.8)	74(41.6)	174(41.1)	0.38(0.22-0.67)	2.567(0.82-8.06)	0.106
>64	70(28.6)	31(17.4)	101(23.9)	0.60(0.36-1.00)	7.45(1.89-29.40)	**0.004**

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

Table 5 Continued

Table 5 Continued

Variables	Causes of Patients hospitalization			Odds Ratios		P-value
	DRH(245) n (%)	Non-DRH(178) n (%)	Total(423) n (%)	COR(95% CI)	AOR(95% CI)	
Marital status						
Single	64(26.1)	34(19.1)	98(23.2)	1.000	1.00	0.300
Married	129(48.6)	105(59)	234(55.3)	0.60(0.37-0.99)	0.60(0.29-1.23)	0.160
Widowed	20(8.2)	9(5.1)	29(6.7)	0.74(0.40-1.39)	0.49(0.20-1.18)	0.109
Divorced	42(17.1)	31(16.9)	73(17.3)	1.18(0.49-2.87)	0.35(0.19-0.75)	0.983
Education level						
No formal education	116(47.3)	72(40.4)	188(44.4)	1.00	1.00	0.183
Elementary	66(26.9)	47(26.4)	113(26.7)	0.87(0.54-1.40)	0.57(0.23-1.43)	0.229
Secondary	31(12.7)	35(19.7)	66(15.6)	0.55(0.31-0.97)	0.57(0.23-1.39)	0.215
Tertiary	32(13.1)	24(13.5)	56(13.2)	0.83(0.45-1.52)	0.36(0.14-0.92)	**0.033**
Employment						
Employed	25(10.2)	25(14)	50(11.8)	1.00	1.00	0.156
Unemployed	0	1(0.6)	1(0.24)	0.48(0.21-1.12)	0.29(0.09-0.89)	1.000
house wife	30(12.2)	33(18.5)	63(14.9)		1.80(0.65-4.98)	0.259
merchant	13(5.3)	14(7.9)	27(6.4)	0.44(0.19-0.98)	1.81(0.56-5.89)	0.325
Student	18(7.3)	7(3.9)	25(5.9)	0.45(0.17-1.20)	6.33(1.38-29.15)	**0.018**
Day laborer	51(20.8)	32(18)	83(19.6)	0.89(0.34-2.29)	2.64(0.99-7.023)	0.051
Retired	57(23.3)	40(22.5)	97(22.9)	0.77(0.35-1.67)	0.98(0.35-2.79)	0.973
farmer	22(9)	12(6.7)	34(8)	1.24(0.42-3.66)	2.89(0.89-9.36)	0.077
Others*	29(11.8)	14(7.9)	43(10.2)	0.69(0.32-1.46)	3.41(1.12-10.37)	**0.031**
Polypharmacy						
Yes	84(34.3)	43(24.2)	127(30)	1.64(1.06-2.53)	1.48(0.72-3.04)	0.284
No	161(65.7)	135(75.8)	296(70)	1.00	1.00	

*Others: participants who did not have any occupation

Table 5 Continued

Table 5 Continued

Variables	Causes of Patients hospitalization			Odds Ratios		P-value
	DRH(245)	Non-DRH(178)	Total(423)	COR(95% CI)	AOR(95% CI)	
	n (%)	n (%)	n (%)			
Co morbid condition						
Yes	137(55.9)	76(42.7)	213(50.4)	1.70(1.15-2.51)	2.00(1.09-3.67)	**0.024**
No	108(44.1)	102(57.3)	210(49.6)	1.00	1.00	
Hospital stays (days)						
1─7	101(41.2)	112(62.9)	213(50.4)	1.00	1.00	
>7	144(58.8)	66(37.1)	210(49.6)	2.42(1.63-3.60)	2.19(1.41-3.38)	**0.000**

DISCUSSION

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

The occurrence of DRHs was high (245,57.9%) and is substantially utmost from other studies conducted in America (16.2%), Brasil(31.6%) , Denmark (10.8%) ,Norway(38%),Sewdin (41.3%),Greece(12.8%) %,India(17.2 %), and Malaysia (39%).[3 5 6 16-18 24 25] The high prevalence in the current study could be explained by numbers of reasons:(1) The categories of DRPs causing DRHs investigated in the present study were comprehensive, whilst other studies only investigated particular types of DRPs resulted DRHs such as therapeutic failure[25] and ADR [2 24 26 27]; (2) the prospective design of this study helps to ensure that all information required to accurately classify

the events were gathered;(3)detailed histories of drug therapy obtained by clinical pharmacists may improve detection of DRHs ;and(4) use of the Helper's and Strand's comprehensive classification system has likely boosted the probability that all possible drug-related causes of hospitalization to be identified. Largely, the wide variability in the rate of DRHs may be attributed to the variations in the extent of study population, inclusion criteria, study settings, participant's level of education and awareness, level of health professional expertise, methods of evaluating DRHs attributed to DRPs, study designs (prospective vs. retrospective) and the study duration. These variations of reasons also reported by other studies. [2 9 10 26 27]

In this study, 87.8 % of DRHs were deemed to be preventable which is agreed with other international studies in which preventability of DRHs has been by far greater than fifty percent. [9-11 16 19 20 27 28] In the present study, the reasons why DRHs preventability has been high due to they have not been appeared, if possible, measurements could be taken prior to drug related diseases. For instance, the principal categories of DRHs in our study were failure to receive drugs (130,53.5%) and untreated indication (94, 38.5%). Hence, both DRHs attributed to DRPs could be avoided by providing awareness for patients about their drugs use, applying good prescribing and dispensing practice, and providing appropriate pharmaceutical care plan.

The majority of DRHs were most commonly seen among female patients, which is concordant with what has been done in the previous study. [29] However, in study done in Saudi Arabia, DRHs were largely found in male patients.[2 20] Elderly patients developed more DRPs leading to DRHs than patients in other age groups which also in line with other studies. [5 25 30] The main reasons could be as patient's age is becoming advanced; physiologic functions are being deteriorated and presence of likelihood of co morbid conditions which may predispose them to taking of multiple drugs concomitantly which ultimately basis for the patients to contract medication side effects, interactions (drug-drug or drug-food) thereby failure to receive drugs will occur owing to patients

non-adherence to their regimens, fear of drugs side effect, unavailability and expensiveness of the drugs.

In this study,patients whose education level being elementary and below were more prone in developing DRHs than having education high school or above which was consistent with studies done previously. [3 16]This could be related to high level education might be useful to understand about appropriate medications use. More than half of DRHs also accounted from patients whose occupations were day laborer, retired and patients lived in dependency stated as others in

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

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Gender			
Male	119(48.6)	88(49.4)	207(48.9)
Female	126(51.4)	90(50.6)	216(51.1)
Age (in years)			
Mean± SD	48.23±17.85		
14 - 24	24(9.8)	14(7.9)	38(8.98)
25- 39	51(20.8)	59(33.1)	110(26)
40 - 64	100(40.8)	74(41.6)	174(41.1)
>64	70(28.6)	31(17.4)	101(23.9)
Marital status			
Single	64(26.1)	34(19.1)	98(23.2)
Married	129(48.6)	105(59)	234(55.3)
widowed	20(8.2)	9(5.1)	29(6.7)
Divorced	42(17.1)	31(16.9)	73(17.3)
Education level			
No formal education	116(47.3)	72(40.4)	188(44.4)
Elementary	66(26.9)	47(26.4)	113(26.7)
Secondary	31(12.7)	35(19.7)	66(15.6)
Tertiary	32(13.1)	24(13.5)	56(13.2)
Residence			
Addis Ababa	177(72.2)	127(71.3)	304(71.9)
Out of Addis Ababa	68(27.8)	51(28.7)	119(28.1)
Religion			

Orthodox	186(76)	136(76)	322(76.1)
Muslim	42(17.1)	31(17.4)	73(17.3)
Catholic	1(0.4)	1(0.6)	2(0.5)
Protestant	16(6.5)	10(6)	26(6.1)

DRHs, drug related hospitalizations; non-DRHs, non-drug related hospitalizations; SD, standard deviation

Table 1 … Continued

Table 1 …. continued

Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Employment			
Employed	25(10.2)	25(14)	50(11.8)
Unemployed	0.0	1(0.6)	1(0.24)
House wife	30(12.2)	33(18.5)	63(14.9)
Merchant	13(5.3)	14(7.9)	27(6.4)
Student	18(7.3)	7(3.9)	25(5.9)
Laborer	51(20.8)	32(18)	83(19.6)
Retired	57(23.3)	40(22.5)	97(22.9)
Others	29(11.8)	14(7.9)	43(10.2)
Farmer	22(9)	12(6.7)	34(8)
Social habit (smoking cigarette)			
Yes	29(11.8)	15(8.4)	44(10.4)
No	216(88.2)	163(91.6)	379(89.6)
Social habit (dining alcohol)			
Yes	71(29)	57(32)	128(30.3)
No	174(71)	121(68)	295(69.7)
Physical activity(walk)			
Yes	165(39)	127(71.3)	292(69)
No	80(32.7)	51(28.7)	131(31)
Physical activity (regular physical exercise)			
Yes	5(2)	5(2.8)	10(2.4)
No	240(98)	173(97.2)	413(97.6)

[2] Others: participants who did not have any occupation rather they were dependent to live with other people. DRH, drug related hospitalization; Non-DRH, Non-drug related hospitalization; n, number; SD, standard deviation

Table 1 …. continued

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Other Drugs (including OTC, herbals)			
Yes	3(1.2)	0(0)	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Number of medications taken per patient			
Mean± SD	3.39±2.35		
0	24(9.8)	12(6.7)	36(8.5)
1	41(16.7)	26(14.6)	67(15.8)
2	35(14.3)	40(22.5)	75(17.7)
3-5	98(40)	75(42.1)	173(40.9)
>5	47(19.2)	25(14)	72(17)
Polypharmacy			
Yes	84(34.3)	43(24.2)	127(30)
No	161(65.7)	135(75.8)	296(70)
Co morbid condition			
Yes	137(55.9)	76(42.7)	213(50.4)
No	108(44.1)	102(57.3)	210(49.6)
Co morbid condition (Hypertension)			
Yes	68(27.8)	40(22.5)	108(25.5)
Co morbid condition (Diabetes mellitus)			
Yes	31(12.7)	22(12.4)	53(12.5)
Co morbid condition (Cardiac diseases)			
38(15.5)	21(11.8)	59(13.9)	
Length of Hospital stay (Days)			
1—7	101(41.2)	112(62.9)	213(50.4)
>7	144(58.8)	66(37.1)	210(49.6)
Mean± SD	11.4±9.27		
Median	9		
Range	2-96		

.It could be associated with that of they could not afford their drugs and cultural issue.

Of the 245 patients with DRHs, the foremost category of DRHs in this study was failure to receive drugs (130,53.5%) followed by untreated indication (94,38.5%),adverse drug reaction(38,15.5%) and sub therapeutic dosage (30,12.2%).The findings were reported by other studies.[11 16 18-20 23 25 28 31]The major reasons for failure to receive drugs in present study were patients prefer not to take the drugs rather they preferred others cultural and religious therapy activities, drug products were not available, cost of medications was too expensive, fear of adverse events, failure to follow-up due to Covid-19, and they felt better and near to half of patients with DRHs were illiterate. Therefore, inability to recall the regimen were other important reasons associated with increased risk of a hospitalization related to failure to receive drugs which was mentioned in the past studies.[3 10 19]

The second frequent category of DRHs was untreated indication (94, 38.5%) as it was reported in other studies.[8 20] Reasons were patients remained untreated; prophylaxis and synergistic medications were not indicated. This might be due to incorrect diagnosis; patients didn't come to health setting timely and treating physicians did not follow the management guidelines/protocols. For example, patients having moderate persistent asthma were being treated with albuterol inhalation alone and statins have not been indicated for patients with atherosclerotic cardiovascular disease (ASCVDs) like peripheral arterial disease, stroke, ischemic heart disease and whose age ≥ 40 years with diabetes mellitus and high low density lipoprotein level. In addition, some compelling indication like hypertension remains untreated and subsequently results in DRHs owing to stroke and others cardiovascular diseases. Furthermore, since only cancer diagnosis and management are carried out in one of this research setting hospital which is TASH, patients come from different Ethiopia places were remained untreated and predisposed to various empirical therapies that also lead to improper drug selection until they treat with anti-cancer drugs in TASH.

ADRs (38, 15.5%) were also commonly reported as the common classifications of DRHs which is also mentioned with other studies. [10 17-19 27 28 32] This might be associated numerous numbers of cardiac and diabetic patients in our study population and poor awareness of patients with regard to cardiac medications untoward effects such as diuretics inducing electrolytes disturbance and hypoglycemic symptoms of antidiabetics, respectively might be plausible explanations for increased ADRs. Some ADRs could be resulted from disobeying of direction for use of the medications. For example, diabetes mellitus patient who was on metformin experienced epigastric burning sensation pain and vomiting after metformin was being taken without meal. Overall, the plausible explanations for DRHs might be the absence of pharmaceutical care services in many health institutions including those wards of the study settings that is very important to optimize drug therapy and patient safety and also there were a poor collaboration among patients, clinical pharmacists and physicians about patient's medications use process involving medications use, their side effects, adherence issue and consequences if they will not take their medication properly. Therefore, the better opportunity for clinical pharmacists to add value in patient care roles is through ensuring medication management services according to evidence-based guidelines. Both failure to receive drugs and untreated indication for which need additional drug therapy were mentioned in the present study as a main categories of DRPs resulted DRHs were supported by other study.[6 8 16]

In this study finding, medication classes that were frequently reported as causing of DRHs were cardiovascular medicines, chemotherapeutic drugs, endocrine drugs, respiratory medicines and central nervous system drugs. Among these classes of drugs, cardiovascular drug were predominantly involved in DRHs which was in line with other studies.[3 5 19 23 25 31] Cardiovascular drugs, antidiabetics, and antiasthmatics were most commonly associated with DRHs was supported in the previous studies.[2 22 24 25] The most common drugs associated with DRHs

mentioned in this study finding were furousemide, ACEIs ,insulins, oral hypoglycemic agents, warfarin, spironolactone ,aspirin and central nervous system agent and those were implicated in the previous studies. [6 9 19 20 22 27 31] The main reason might be connected with the common diseases of the study area which were heart failure, diabetes mellitus, stroke, human immunodeficiency virus and asthma. For those diseases, the above-mentioned drugs have been participated.

Moreover, the most common organ system involved in DRHs was the cardiovascular system (80, 32.6%), with the most common specific disease of heart failure (55, 22.5%) which is consistent with the previous studies. [5 23] Moreover, hypertension was mentioned for DRHs which was implicated in the previous study. [20 25 31] This is due to cardiovascular diseases require multiple medicine regimens and this contributed to DRPs. Among hospitalized patients attributed to endocrine systems were due to hypoglycemia, hyperglycemia and diabetic ketoacidosis which was also cited in the other study.[20 25] It might be due to the patients poor awareness about the hypoglycemic symptoms of anti-hypoglycemic agents , poor monitoring control and patients prefer not to take the medications.

In this study, age, educational level, length of hospital stays and presence of co morbid disease had statistically significant correlation with the occurrence of DRHs. The findings are consistent with other studies.[16 18 28 29]

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

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

The other factor was education level in which patients with tertiary education level were 64% less likely to be hospitalized with drug related hospitalizations as compared to participants who did not have formal education. This could be related to high level education might be useful to understand about appropriate medications use. This was supported by the studies conducted at Brasil. [3 10 16] Patients with co morbid disease were also 2 folds high likely to be drug related hospitalized than non-drug related as compared to patients without co morbid disease. As implicated in the previous studies,[16 28 29] co- morbidity increases the vulnerability towards DRPs. These results clearly indicate the necessity of managing DRHs in multimorbid patients.

For patients who stayed > 7dasy in hospital due to admission were 2.4 times more likely to develop DRHs compared to patients who admitted due to non-DRHs with estimated to < 7 days of length of hospital stay. In terms of drug related hospital stay, the overall length of the hospital stay in the present study was 2788 days with the average length of hospital stay 11.4±9.27 days, which is longer than what has been reported in other study [11].This was might be owing to the data in the previous study is in a single hospital and for a relatively short period of time (28 days)while in this finding, the study was carried out at three tertiary care hospitals for the periods of 60 days.

Therefore, avoiding preventable DRHs is also a very cost-effective tool for health care systems and could reduce the problem of bed crisis in hospitals.

Among factors which have not demonstrated an association in multivariate analysis, polypharmacy was mentioned. This agree with what have been reported in other studies[19 23].In contrast, polypharmacy has been reported having positive association with the occurrence of DRHs in the previous literatures[3 5 10 19 20 28].This insignificance could be resulted from variations in numbers of used medications and identified DRPs for causing DRHs. In this study, around two third of the patients with DRHs were used from none to four drugs per patient. Accordingly, to say polypharmacy; ≥ five drugs should be concomitantly taken. Furthermore, the identified DRPs causing DRHs were failure to receive drugs and untreated indication. So, both categories reveal not taking medications and the patients might not use polypharmacy. Additionally; marital status did not illustrate significant association with DRHs.

This study has some limitations. One of the main limitations of this study was there are no standardized protocols for immediately recording and reporting DRHs which may limit the estimation of real drug related hospitalized cases and leads to discrepancy of actual DRHs. This problem was mitigated by using clinical pharmacists who have an ability to identify and resolve DRPs. A factor limiting the scope of this study concerned patients admitted to an EW. Hence, considerable numbers of patients with DRPs from other major departments have been missed. Though, during the data collection period, patients brought to health institutions were decreased owing to covid-19 epidemic, being this study multicenter has been able to obtain large sample size.

Conclusion

The prevalence of DRHs was relatively high among emergency ward patients in the study settings. Failure to receive drugs and untreated indication were the most frequently reported categories of

DRHs. Of drugs, cardiovascular drugs and drugs acting on the endocrine system have been the most frequently implicated drugs in patients with DRHs. Amid factors; Age, educational level, participants who did not have any occupation, presence of co-morbid condition and hospital stay have had significant association with DRHs. Hence, researches regarding DRHs should be conducted in different Ethiopian hospitals to demonstrate its impact. Categories DRHs in patients' medical chart should be appropriately recorded and to improve quality health services, clinical pharmacy services should be delivered in different wards of the hospitals. Medication use counseling and education are needed for chronic disease patients. Therefore, patients, caregivers/families, nurses, physicians and pharmacists should be collaborating more closely to provide and reinforce pharmaceutical care and monitor patients to prevent drug related emergency department visits and subsequent morbidity and mortality.

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Contributors

ABB and MBD contributed to conceptualization, design, analysis and write up. MBD organized the collection of data for analysis and write up the draft manuscript. ABB and MBD supervised the collection data and overall research work including interpretation of results, reviewed and

revised critically the manuscript. Both authors approved the final version to be submitted for publication.

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Supporting information

S 1 File:Data collection tool.docx

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

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

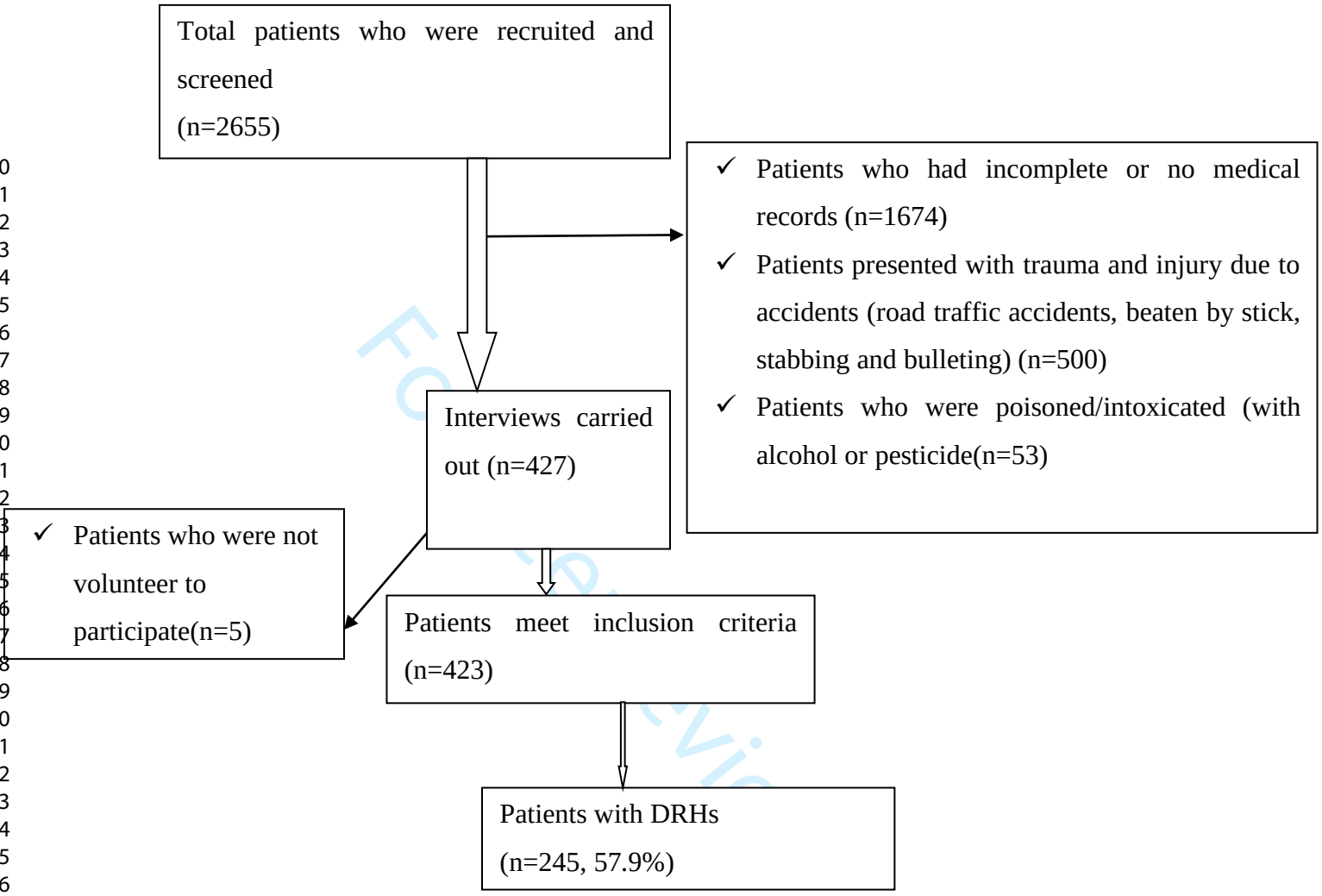

Figure 1

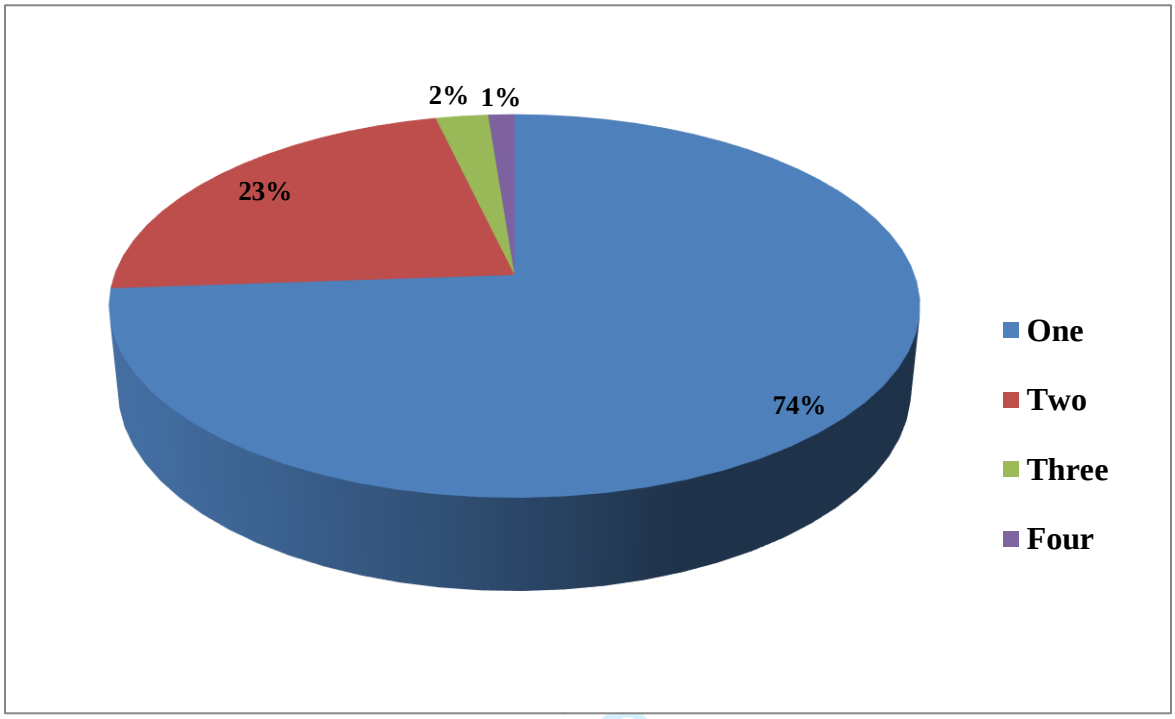

Figure 1

Data abstraction formats

Annex 1: Patient's demographic and clinical data

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

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

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

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

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

1. Past medical conditions and medications

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

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

PMH: _____

PSH: _____

Injuries: _____

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

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

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

---

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

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

Any diagnostic tools/Imaging techniques/modalities with findings

Technique	Date(dd/mm/yy)	Date(dd/mm/yy)	Date(dd/mm/yy)

Annex 2: Categories of potentially Preventable Drugs-Related Admission Categories

DTPs Categories	Common Cause of Drug therapy problem
1. Unnecessary drug therapy	☐ No medical indication of the drug is found ☐ Duplication of drug therapy is existed ☐ Non drug therapy should be indicated ☐ Drug is used in treating avoidable ADR ☐ Others ,specify_____
2. Needs additional drug therapy	☐ Untreated medical condition is existed ☐ Preventive/ prophylactic drug needed ☐ Synergistic/ potentiating drug needed ☐ Others, specify_____
3. Ineffective drug product/ Improper Drug Selection	☐ More effective alternative drug is available ☐ Condition is already refractory to drug ☐ Dosage form is inappropriate ☐ The drug is not effective for condition ☐ Others, specify_____
4. Sub therapeutic Dosage.	☐ Wrong dose (too small) of the drug ☐ Frequency is inappropriate (long) ☐ Duration of drug use is too short
5. Over dosage	☐ Wrong dose (too high) of the drug ☐ Frequency is inappropriate (short) ☐ Duration of drug use is too long ☐ Others, specify_____
6. Adverse drug reaction	☐ Undesired effect from the drug is found ☐ Unsafe drug for patient is existed ☐ Dosage is administered or changed too rapidly ☐ Allergic reactions is found/reported ☐ Contraindication to the drug is present ☐ Administered too rapidly
7. Drug Interactions	☐ There is (are) Major drug interaction (s)
8. Failure to Receive Drugs.	☐ Does not understand instructions: the patient does not understand how to properly take or use the drug product and dosage regimen. ☐ Patient prefers not to take ☐ Patient forgets to take ☐ Drug product not available ☐ Cost of medication too expensive ☐ Cannot swallow/administer drug ☐ No willingness to take the drug ☐ Unavailability of medication ☐ Disbelieves on the drug effectiveness ☐ Patient felt better or worse ☐ Fear of adverse events ☐ Regimen complexity

Medication classes	Individual drugs	Types of DRPs

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Prevalence and Predictors of Drug-Related Hospitalizations among Patients Visited Emergency Departments of Addis Ababa City Hospitals in Ethiopia: A Multicenter Prospective Observational Study

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ABSTRACT

Objectives: This study aimed to determine the prevalence, categories and predictors of drug related hospitalizations (DRHs) among patients visited emergency departments of Addis Ababa city hospitals, Ethiopia.

Design: A multicenter prospective observational study was conducted through patients interview and chart review.

Settings: The study was undertaken in three tertiary care hospitals, Addis Ababa, Ethiopia.

Participants: A total of 423 patients fulfilling the inclusion criteria were included.

Outcome measures: Prevalence and preventability of DRHs, categories of drug related problems causing DRHs, medications and diseases involved in DRHs and factors significantly associated with DRHs.

Result: More than half of the patients (216, 51.1%) were females. The mean age (SD) was 47.50 (±17.21) years. The mean length of hospital stay (SD) was 10.29(±8.99) days. Nearly, 60% (249) of them were hospitalized due to drug related problems, of which 87.8% were preventable. The cause for hospitalization for more than half (130, 53%) of them was failure to receive drugs and 37.85 (94) patients were categorized as untreated indications. Age ≥ 65 years (Adjusted Odds Ratio [AOR]=7.451,95%CI: 1.889-29.397), tertiary educational level (AOR=0.360, 95%CI: 0.141-0.923), participants who did not have any occupation (AOR=3.409, 95%CI: 1.120-10.374)

presence of co-morbid conditions (AOR=2.004, 95%CI: 1.095-3.668) and hospital stay > 7 days (AOR=2.186, 95%CI: 1.412-3.382) were predictors of DRHs.

Conclusion: Nearly 90% of DRHs were deemed to be preventable in the study settings. Older age, lower educational level, unemployment, presence of co-morbid condition and staying >7 days in hospital as an inpatient were predictors of DRHs.

Strength and limitations of the study

- To the best of our knowledge this is the first study in the African continent.
- The strength of this study is the study design which is a prospective observational study.
- This is a multicenter study with sufficient sample size, increasing representativeness the findings.
- The main limitation of this study is lack of standardized procedures for immediate recording and reporting of DRHs.
- Patients who visited other than the emergency ward were excluded from participation can also be considered as a limitation of the study.

INTRODUCTION

Though drugs can be ordered for the intention of achieving desired health outcomes that improve patients quality of life, symptoms and signs of diseases causing drug related hospitalizations (DRHs) as a result of drug related problems (DRPs) could be apparent.[1-3] DRP is defined according to Helper and strand as 'an undesired event or circumstance due to drug therapy that actually or potentially interferes with desired health outcomes'.[4]

Medication's use has been increasing across the globe due to the presence of large number of treatable diseases and this has contributed to production of more advanced medications by the pharmaceutical industries. Therefore, advances in drug therapies could lead to an apparent increase in the incidence of DRPs, which in turn lead to hospitalization[5]. Hospitalization can be defined as

drug related if it is straightforwardly linked to one of the eight predefined Helper's and Strand's classifications of DRPs: adverse drug reaction (ADR), drug interaction, improper drug selection, untreated indication, sub-therapeutic dosage, supra-therapeutic dosage, failure to receive drugs, and drug use without indication.[6-12] Those DRPs can arise when a medicine is prescribed aptly and used correctly (e.g., ADR), due to errors involving prescribing (including inappropriate or over-treatment, and failure to prescribe the indicated treatment or under-treatment), dispensing, administering, reconciling, or monitoring of medicines as well as from poor patient adherence.[2 13 14] According to the World Health Organization (WHO), an ADR is any harmful, undesired and inadvertent drug effect that occurs at doses used in human for therapy, diagnosis or prophylaxis.[15]

Over the past decades, DRHs have been considered as wide spreading[16]. In the United States, DRPs accounted for 17 million emergency department (ED) visits and 8.7 hospitalizations annually.[17] It increases morbidity and mortality rates, health care cost, decreases income and household productivity and reduced quality of life.[2 18 19]

Studies carried out in different areas of the globe estimated the extent of DRHs to be between 16% to 41.3%. Of these, 50% to 95% were preventable. Supratherapeutic dosage (10.3%-12.7%), non-compliance (10.6%-65.8%), ADRs (10.7%-45.5%) and untreated indications (10.7-13.3%) were frequently identified as the causes of DRHs.[6 9 18 20-22]

DRPs resulting DRHs were defined as preventable if the patient failed to take a drug that is known to reduce or prevent symptoms according to the prescribed directions, took a drug for which a patient had a known allergy, drug treatment was obviously improper, dosage differed from accepted recommendations, took a drug that was not indicated, and if there was a failure to monitor by a physician at reasonable time intervals due to financial difficulty. If there was, however, no reasonable actions to prevent DRPs, it is then termed as non-preventable.[20 23]

In many studies, patients with DRHs had mainly cardiovascular diseases and diabetes, suggesting that cardiovascular and hypoglycemic medications were involved in DRHs.[6 10 11 18 20 21 24 25] Previous studies also identified polypharmacy, advanced age and comorbid conditions as factors that favor the occurrence of DRHs.[3 6 20 21]

It is thus important to determine DRHs prevalence to improve treatment outcomes and prevent unnecessary admissions. To the best of our knowledge, there are no studies conducted about DRHs in Ethiopia. The present study therefore aimed to determine the prevalence, categories and predictors of DRHs among patients admitted to an ED of three selected hospitals in Addis Ababa, the capital of Ethiopia.

METHODS

Study Settings

The study was carried out in the ED of Tikur Anbessa Specialized Hospital (TASH), Zewditu Memorial Hospital (ZMH), and Yekatit 12 Hospital Medical College (Y12HMC), Addis Ababa, Ethiopia. TASH has 700 beds and it is a tertiary care teaching hospital affiliated with Addis Ababa University. In TASH, outpatient, inpatient, and emergency services are delivered. The ED provides services for about 13,920 patients per year. Y12HMC is also a tertiary carry level referral and teaching hospital that provides both inpatient and outpatient treatment for a large number of people coming from Addis Ababa as well as other places of the country. The hospital has a total of three ED rooms. The adult medical ED is collocated with adult surgical ED. It serves around 10,560 patients per year. The third hospital is ZMH, which is one of the teaching and general referral hospitals in Ethiopia and the ED serves about 10,560 patients per year.

Patient involvement

Patients did not participate in the initial conception and design of the study. However, based on the participating patients' comments during the pretest (5% of the sample size), we made a correction on the patient approach and timing for an interview at ED during data collection. Patients who participated actively in this study determined the medication use, level of adherence, and medical history.

Study design and population

A prospective observational study design was used to collect data from August to September, 2020. All patients admitted to the ED of the three selected hospitals during the study period and fulfilled the inclusion criteria were included.

Inclusion and exclusion criteria

Patients having a medical history with completed data and ≥ 14 years old were included. Patients with incomplete or no medical records, refused to participate, presented with trauma and injuries associated with accidents (e.g. road traffic accidents, beaten by stick, stabbing and bulleting) and poisoned/intoxicated (for instance snake bite, alcohol intoxication or use of pesticide) were excluded. During data collection periods, about 2655 patients were being admitted to the ED, out of which 423 participants fulfilled the inclusion criteria

Sample size determination and techniques

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

$n = [(Z\ \alpha/2)^2 \times p\ (1-p)] \vee d^2 = [(1.96)^2 x0.5x0.5] / 0.05^2 = 384$

(Hence; n = required sample size, Zα/2 = critical value for normal distribution at 95% confidence interval, which equals 1.96 (*Z* value at alpha = 0.05), P = Proportion of DRH =0.5, d = margin of

error of 5%=0.05. The calculated sample size using this formula was 384. Adding 10% contingency (for non-response rate) to compensate participants who could refuse to participate, brought the final sample size to 423. The sample size was distributed to the three hospitals based on the patient load of hospital's ED per annum as mentioned in the Study settings. Accordingly, 169 participants were included from TASH, 127 participants from ZMH and 127 participants from Y12MHC.

Data collection procedures

A structured questionnaire was developed from carefully evaluated published articles in the literature. For instance, categories of DRPs that leads to hospitalization and factors having association with DRH (e.g. socio-demographic and clinical characteristics) were extracted from literatures. All the necessary data including patients' demographic details (age, sex, marital status, education level, employment), and clinical information like the number of medications being taken prior to admission were collected and documented using a data collection tools through interviewing the patients. Furthermore, patient's medical records were reviewed by data collectors to obtain clinical information (disease history, allergic status, admission diagnosis, length of hospital stay during admission, number of medications being taken prior to admission, data on laboratory investigations). Supplementary information and clarifications on some patient's medical information were obtained through discussion with the treating physicians and residents. By applying those data gathering approach, different categories of DRPs resulting hospitalization with their possible causes were determined.

Data were collected by three pharmacists having Master of Science degrees in Clinical Pharmacy. They had basic knowledge and skill in pharmaceutical care services and also received training on how to obtain data from patients' medication charts and approach the patients and health care professionals. Updated Ethiopian Standard Treatment Guidelines for Hospitals, third edition, 2014, Ethiopian Antiretroviral Therapy and Tuberculosis Guidelines, Cancer Treatment Protocols prepared by TASH Oncologists, Pharmacotherapy textbooks, Medscape, UpToDate were used as a guide for diseases management. Micromedex online database was used to check drug

interactions. Furthermore, updated guidelines released from American Cardiology Center, American Heart Association, European Cardiology Society, American Diabetic Association were used as a guide to treat different diseases. Clinical pharmacists along with physicians determined subtherapeutic and supratherapeutic dosage outcomes using medical charts, laboratory tests, clinical outcomes, medication dose and frequency. Participant's hospitalization attributed to failure to receive drugs was decided using physician's recording documentation, clinical pharmacists' knowledge and patients reporting evidence. Untreated indications and improper drug selection were evaluated and interpreted using treatment guidelines. For instance, if patients presented with untreated or improperly treated cardiac diseases, treatment was initiated and optimized using the American Heart Association guidelines, and UpToDate latest version. To minimize bias, the three pharmacists at each hospital independently evaluated the identified DRPs resulted hospitalizations. Decision was then reached by reaching consensus after a series of meetings and discussions as well consultations with physicians and residents. Once DRPs resulting DRHs were identified, they were recorded and classified using DRPs registration format according to Helper's and Strand's classification.

Data collection management

Pretest was performed on 5% patients in TASH prior to the actual data collection period and amendment was made accordingly. The data collection process was supervised, and the information gathered via data abstraction formats were reviewed and cheeked for their completeness every day to ensure quality. Urgent correction was made, if any errors were identified.

Data analysis

The data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 26. Mean and standard deviation for continuous variables and frequency and percentage for

categorical variables were computed by using descriptive statistics in SPSS to summarize socio-demographic and relevant clinical characteristics of the study participants. Tables and charts were used to present the results. Furthermore, univariate and multiple binary logistic regressions were performed to analyze factors that predict DRHs. Variables with p-values < 0.2 in the binary univariate analysis were included in the multiple binary logistic regressions to control the effect of confounders. The level of significance was set at p–value ≤ 0.05 and results were reported as odds ratios (OR) with 95% confidence intervals.

RESULTS

Socio-demographic and clinical characteristics

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

Socio-demographic and clinical characteristics of the participants is depicted in

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

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Gender			
Male	119(48.6)	88(49.4)	207(48.9)
Female	126(51.4)	90(50.6)	216(51.1)
Age* (in years)			
Mean± SD	48.23±17.85	46.5±16.3	47.5±17.2
14 - 24	24(9.8)	14(7.9)	38(8.98)
25- 39	51(20.8)	59(33.1)	110(26)
40 - 64	100(40.8)	74(41.6)	174(41.1)
>64	70(28.6)	31(17.4)	101(23.9)
Marital status*			
Single	64(26.1)	34(19.1)	98(23.2)
Married	129(48.6)	105(59)	234(55.3)

widowed	20(8.2)	9(5.1)	29(6.7)
Divorced	42(17.1)	31(16.9)	73(17.3)
Education level*			
No formal education	116(47.3)	72(40.4)	188(44.4)
Elementary	66(26.9)	47(26.4)	113(26.7)
Secondary	31(12.7)	35(19.7)	66(15.6)
Tertiary	32(13.1)	24(13.5)	56(13.2)
Residence			
Addis Ababa	177(72.2)	127(71.3)	304(71.9)
Out of Addis Ababa	68(27.8)	51(28.7)	119(28.1)
Religion			
Orthodox	186(76)	136(76)	322(76.1)
Muslim	42(17.1)	31(17.4)	73(17.3)
Catholic	1(0.4)	1(0.6)	2(0.5)
Protestant	16(6.5)	10(6)	26(6.1)

DRHs, drug related hospitalizations; non-DRHs, non-drug related hospitalizations; SD, standard deviation;

* Represent variables having significant bivariate associations.

Table 1 …. continued

Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Employment status*			
Salaried worker	111(45.3)	83(46.6)	194(45.9)
Unemployed	87(35.5)	74(41.6)	161(38.1)
Student	18(7.3)	7(3.9)	25(5.9)
Other	29(11.8)	14(7.9)	43(10.2)
Social habit (smoking cigarette)			
Yes	29(11.8)	15(8.4)	44(10.4)
No	216(88.2)	163(91.6)	379(89.6)
Social habit (drinking alcohol)			
Yes	71(29)	57(32)	128(30.3)
No	174(71)	121(68)	295(69.7)
Any physical activity			
Yes	170(69.4)	132(74.1)	302(71.4)
No	70(30.6)	46(25.9)	106(28.6)

[2] Others: participants who did not have any occupation rather they were lived as dependent with other people. DRH, drug related hospitalization; Non-DRH, Non-drug related hospitalization; n, number; SD, standard deviation

* Represent variables having significant bivariate associations.

Table 1 …. continued

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Home remedies (herbals)			
Yes	3(1.2)	0(0)	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Number of medications taken per patient *			
Mean± SD	3.4±2.4	3.2±2.1	3.3±2.3
0	24(9.8)	12(6.7)	36(8.5)
1	41(16.7)	26(14.6)	67(15.8)
2	35(14.3)	40(22.5)	75(17.7)
3-4	61(24.9)	57(32)	118(27.9)
≥5	84(34.3)	43(24.2)	127(30)
Polypharmacy			
Yes	84(34.3)	43(24.2)	127(30)
No	161(65.7)	135(75.8)	296(70)
Co morbid condition*			
Yes	137(55.9)	76(42.7)	213(50.4)
No	108(44.1)	102(57.3)	210(49.6)
Co morbid condition (Hypertension)			
Yes	68(27.8)	40(22.5)	108(25.5)
Co morbid condition(Diabetes mellitus)			
Yes	31(12.7)	22(12.4)	53(12.5)
Co morbid condition (Cardiac diseases)			
Yes	38(15.5)	21(11.8)	59(13.9)
Length of Hospital stay (Days) *			
1–7	101(41.2)	112(62.9)	213(50.4)
>7	144(58.8)	66(37.1)	210(49.6)

. More than half of the participants (216, 51.1%) were females. The mean (SD) age of the participants was 47.5 (±17.21) years and nearly two third (275, 65%) were ≥ 40 years of age. More than 70 % (301, 71.1%) of the total participants' level of education was below secondary school. Nearly three-quarter of them (304, 71.9%) resided in Addis Ababa city. Out of the total study participants, 58% (245) of them were taking ≥3 and 30% (127) ≥ five drugs prior to admission, which is termed as polypharmacy. Above half of the participants (213, 50.4%) had co-morbid diseases, including hypertension (108, 22.5%), cardiac diseases (59, 13.5%) and diabetes mellitus (53, 12.5%). The total length of hospital stay was 4352 days with a mean (SD) of 10.28±8.99 days and ranges from 2 to 96 days.

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

Variables	[1]DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Gender			
Male	119(48.6)	88(49.4)	207(48.9)
Female	126(51.4)	90(50.6)	216(51.1)
Age* (in years)			
Mean± SD	48.23±17.85	46.5±16.3	47.5±17.2
14 - 24	24(9.8)	14(7.9)	38(8.98)
25- 39	51(20.8)	59(33.1)	110(26)
40 - 64	100(40.8)	74(41.6)	174(41.1)
>64	70(28.6)	31(17.4)	101(23.9)
Marital status*			
Single	64(26.1)	34(19.1)	98(23.2)
Married	129(48.6)	105(59)	234(55.3)
widowed	20(8.2)	9(5.1)	29(6.7)
Divorced	42(17.1)	31(16.9)	73(17.3)
Education level*			
No formal education	116(47.3)	72(40.4)	188(44.4)
Elementary	66(26.9)	47(26.4)	113(26.7)
Secondary	31(12.7)	35(19.7)	66(15.6)
Tertiary	32(13.1)	24(13.5)	56(13.2)
Residence			

Addis Ababa	177(72.2)	127(71.3)	304(71.9)
Out of Addis Ababa	68(27.8)	51(28.7)	119(28.1)
Religion			
Orthodox	186(76)	136(76)	322(76.1)
Muslim	42(17.1)	31(17.4)	73(17.3)
Catholic	1(0.4)	1(0.6)	2(0.5)
Protestant	16(6.5)	10(6)	26(6.1)

DRHs, drug related hospitalizations; non-DRHs, non-drug related hospitalizations; SD, standard deviation;

* Represent variables having significant bivariate associations.

Table 1 …. continued

Variables	**DRHs (245), n (%)**	**Non-DRHs (178), n (%)**	**Total (423), n (%)**
Employment status*			
Salaried worker	111(45.3)	83(46.6)	194(45.9)
Unemployed	87(35.5)	74(41.6)	161(38.1)
Student	18(7.3)	7(3.9)	25(5.9)
Other[2]	29(11.8)	14(7.9)	43(10.2)
Social habit (smoking cigarette)			
Yes	29(11.8)	15(8.4)	44(10.4)
No	216(88.2)	163(91.6)	379(89.6)
Social habit (drinking alcohol)			
Yes	71(29)	57(32)	128(30.3)
No	174(71)	121(68)	295(69.7)
Any physical activity			
Yes	170(69.4)	132(74.1)	302(71.4)
No	70(30.6)	46(25.9)	106(28.6)

Table 1 …. continued

[2] Others: participants who did not have any occupation rather they were lived as dependent with other people. DRH, drug related hospitalization; Non-DRH, Non-drug related hospitalization; n, number; SD, standard deviation

* Represent variables having significant bivariate associations.

Table 1 …. continued

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Home remedies (herbals)			
Yes	3(1.2)	0(0)	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Number of medications taken per patient *			
Mean± SD	3.4±2.4	3.2±2.1	3.3±2.3
0	24(9.8)	12(6.7)	36(8.5)
1	41(16.7)	26(14.6)	67(15.8)
2	35(14.3)	40(22.5)	75(17.7)
3-4	61(24.9)	57(32)	118(27.9)
≥5	84(34.3)	43(24.2)	127(30)
Polypharmacy			
Yes	84(34.3)	43(24.2)	127(30)
No	161(65.7)	135(75.8)	296(70)
Co morbid condition*			
Yes	137(55.9)	76(42.7)	213(50.4)
No	108(44.1)	102(57.3)	210(49.6)
Co morbid condition (Hypertension)			
Yes	68(27.8)	40(22.5)	108(25.5)
Co morbid condition(Diabetes mellitus)			
Yes	31(12.7)	22(12.4)	53(12.5)
Co morbid condition (Cardiac diseases[3])			
Yes	38(15.5)	21(11.8)	59(13.9)
Length of Hospital stay (Days) *			

1—7	101(41.2)	112(62.9)	213(50.4)
>7	144(58.8)	66(37.1)	210(49.6)

* Represent variables having significant bivariate associations.

Prevalence and categories of drug related hospitalizations

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

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

Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Untreated indications		94(38.5)
	Untreated medical condition is existed	34(36.2)
	Synergistic/ potentiating drug needed	42(44.7)
	Preventive/ prophylactic drug needed	18(19%)
Improper Drug Selection		16(6.5)
	More effective alternative drug is available	6(37.5)
	Condition is already refractory to drug	2(12.5)
	The drug is not effective for condition	6(37.5)
	Others[4]	2(12.5)

[4] Others; patients who were using expired drugs like insulin and albuterol.

Table 2 Continued……

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Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Sub therapeutic Dosage		30(12.2)
	Wrong dose (too small) of the drug	24(80)
	Frequency is inappropriate (long)	5(16.7)
	Duration of drug use is too short	1(3.3)
Supra therapeutic Dosage		13(5.3)
	Wrong dose (too high) of the drug	11(84.6)
	Frequency is inappropriate (short)	2(15.4)
Adverse drug reaction		38(15.5)
	Undesired effect from the drug is found	34(89.5)
	Unsafe drug for patient is existed	1(2.6)
	Dosage is administered too rapidly	1(2.6)
	Allergic reactions is found/reported	2(5.3)
Drug Interactions		1(0.4)
	There is (are) major drug interaction	1(100)

[5]Others; patients who were using expired drugs like insulin and albuterol.

Table 2 Continued…..

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Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Failure to receive drugs.		130(53.5)
	Does not understand instructions	6(4.6)
	Patients prefer not to take	43(33.1)
	Patients forget to take	3(2.3)

	Drug product not available	17(13.1)
	Cost of medication too expensive	16(12.3)
	Disbelieves on the drug effectiveness	1(0.8)
	Patients felt better	17(13.1)
	Patients felt worse	1(0.8)
	Fear of adverse events	18(13.8)
	Failure to follow-up due to Covid-19	8(6.2)
Total number of DRPs leading DRHs		322
Total number of participants with DRHs		245
Average number DRPs per patients with DRHs		1.31
Preventability of DRHs		215(87.8)

Medications and diseases involved in drug related hospitalizations

Out of a total of 245 drug related hospitalized patients, nearly one -third of them had cardiovascular diseases (80, 32.6%) followed by endocrine disorders (47, 19.2%) and cerebrovascular disease (26, 10.6%).

Table 3: Diseases that associated with drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

Disease's categories	**n(%)**
Cardiovascular diseases	80 (32.6%)
CNS diseases	8 (3.2%)
Cerebrovascular disease	26(10.6%)
Infectious diseases	21 (8.5%)
Endocrine system diseases	47 (19.2%)
Diseases of cancer	25 (10.1%)
Diseases of the respiratory system	21 (8.5%)
GI diseases	10 (4%)
Others*	7 (2.8%)

*Includes anemia, chronic kidney disease, systemic lupus erythematosus and hemophilia

Medication classes and specific drugs implicated in DRHs are depicted in Table 4.

A total of 497 drugs were implicated in 245 drug-related hospitalized patients, providing an encounter of 2.03 drugs per drug-related hospitalized patient. Cardiovascular, antimicrobial, antineoplastic and endocrine drug classes were the most frequently involved drugs in the hospital admissions. Among cardiovascular drugs; furosemide (59,24.1%), angiotensin converting enzyme inhibitors (ACEIs) (48,19.1%), and antiplatelets & anticoagulants (44,18%) were the most frequently mentioned followed by drugs acting on the endocrine system like oral hypoglycemic agents (37, 15.1%) and insulin (24, 9.8%). Antibiotics (25 ,10%), anticancer drugs (23 ,9%), and combination antiretroviral therapy (15, 6.1%) had also contributed to admission to varied extent.

Table 4: Medication classes and specific drugs implicated in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

Drugs class	Specific drugs	n (%)
Cardiovascular drugs		
	Atorvastatin	31(12.7)
	Antiplatelets(aspirin,clopidogril)	24(9.8)
	Furosemide	59(24.1)
	Spironolactone	33(13.5)
	Anticoagulants (Warfarin, heparin)	20(8.2)
	Beta blockers (metoprolol,atenolol)	21(8.6)
	Digoxin	15(6.1)
	Angiotensin converting enzyme inhibitors (enalapril/lisinopril)	48(19.6)
	Calcium channel blockers (nifedipine, amlodipine)	34(13.9)
	Hydrochlorothiazide	11(4.5)

Table 4Continued……..

Table 4 continued…..

Drugs class	Specific drugs	n (%)
Drugs act on the respiratory system		
	Long-acting beta blockers	15(6.1)
	bronchodilator	10(4.1)
Central nervous system drugs		
	Antiepileptics	5(2)
	antipsychotic	5(2)
	Amitriptylin	2(0.8)
Antimicrobial drugs		
	Antibiotics (piperacillin/tazobactam, meropenem, amoxicillin, amoxicillin /clavunicacid ,ceftriaxone, benzathine penicillin)	25(10.2)
	Combination antiretroviral therapy	15(6.1)
	Anti-tuberculosis	13(5.3)
Antineoplastic agents	Cyclophosphamide, imatinib, methotrexate, doxorubicin	23(9.4)
Immuno-suppressants		
	Mycophenolate	1(.4)
	corticosteroids (prednisolone, budesonide)	9(3.7)
Endocrine drugs		
	Oral hypoglycemic drugs (metformin, glibenclamide)	37(15.1)
	Insulin	24(9.8)
	Propylthiouracil	4(1.6)
Gastrointestinal drug	Proton pump inhibitors	7(2.9)
Others	Potassium chloride	1(0.4)
	Non-steroidal anti-inflammatory drugs	3(1.2)
	Opioid	1(0.4)

Table 4 **Continued**

Drugs class	Specific drugs	n (%)
Others		
	Ferrous sulphate	1(0.4)
Total number of medications involved in DRHs		497
Total number of participants with DRHs		245(57.9)
Average number medications per patients with DRHs		2.03

Factors associated with the occurrence of drug related hospitalizations

According to the multivariate logistic regression analysis, five variables such as age, employment, presence of co morbid diseases, length of hospital stay and education level were significantly associated with the occurrence of DRHs (See in Table5). Age > 64 years (Adjusted Odds Ratio [AOR] = 7.451, 95%CI: 1.889-29.397), tertiary educational level (AOR=0.360, 95%CI: 0.141-0.923), participants who did not have any occupation (AOR=3.409, 95%CI: 1.120-10.374), students (AOR=6.331,95%CI:1.375-29.153) presence of co-morbid diseases (AOR=2.004,95%CI: 1.095-3.668), and hospital stay > seven days (AOR=2.186, 95%CI: 1.412-3.382) were predictors of DRHs.

Table 5:**Predictors that involved in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)**

	Predictors of Patients hospitalization			**Odds Ratios**	
	[5]DRH(245)	**Non-DRH(178)**	**Total(423)**	**AOR(95% CI)**	**P-value**
Variables	**n (%)**	**n (%)**	**n (%)**		
Age (Years)					
Mean±SD	48.24±17.86		47.50±17.21		
14 - 24	24(9.8)	14(7.9)	38(8.98)	1.000	0.006
25- 39	51(20.8)	59(33.1)	110(26)	1.55(0.51-4.66)	0.435
40 - 64	100(40.8)	74(41.6)	174(41.1)	2.567(0.82-8.06)	0.106
>64	70(28.6)	31(17.4)	101(23.9)	7.45(1.89-29.40)	**0.004**
Marital status					
Single	64(26.1)	34(19.1)	98(23.2)	1.00	0.300
Married	129(48.6)	105(59)	234(55.3)	0.60(0.29-1.23)	0.160
Widowed	20(8.2)	9(5.1)	29(6.7)	0.49(0.20-1.18)	0.109
Divorced	42(17.1)	31(16.9)	73(17.3)	0.35(0.19-0.75)	0.983
Education level					
No formal education	116(47.3)	72(40.4)	188(44.4)	1.00	0.183
Elementary	66(26.9)	47(26.4)	113(26.7)	0.57(0.23-1.43)	0.229
Secondary	31(12.7)	35(19.7)	66(15.6)	0.57(0.23-1.39)	0.215
Tertiary	32(13.1)	24(13.5)	56(13.2)	0.36(0.14-0.92)	**0.033**

[10]DRH, drug related hospitalization; non-DRH, non-drug related hospitalization; AOR, adjusted odds ratio; CI, confidence interval

Table 5 Continued

	Predictors of Patients hospitalization			Odds Ratios	
	DRH(245)	**Non-DRH(178)**	**Total(423)**	**AOR(95% CI)**	**P-value**
Variables	**n (%)**	**n (%)**	**n (%)**		
Employment status					
Salaried worker	111(45.3)	83(46.6)	194(45.9)	1.00	0.156
Unemployed	87(35.5)	74(41.6)	161(38.1)	0.29(0.09-0.89)	1.000
Student	18(7.3)	7(3.9)	25(5.9)	6.33(1.38-29.15)	**0.018**
Others*	29(11.8)	14(7.9)	43(10.2)	3.41(1.12-10.37)	**0.031**
Polypharmacy					
Yes	84(34.3)	43(24.2)	127(30)	1.48(0.72-3.04)	0.284
No	161(65.7)	135(75.8)	296(70)	1.00	
Co morbid condition					
Yes	137(55.9)	76(42.7)	213(50.4)	2.00(1.09-3.67)	**0.024**
No	108(44.1)	102(57.3)	210(49.6)	1.00	
Hospital stays (days)					
1–7	101(41.2)	112(62.9)	213(50.4)	1.00	
>7	144(58.8)	66(37.1)	210(49.6)	2.19(1.41-3.38)	**0.000**

*Others: participants who did not have any occupation

DISCUSSION

The aim of optimizing pharmacotherapy is to achieve the desired therapeutic outcomes in the absence of morbidity and mortality associated with a drug. To the best of our knowledge, this study is the first to explore the prevalence, categories and rate of preventability of DRHs in the ED of three selected hospitals that are responsible for the provision of medical and surgical care to patients in need of immediate care.

The occurrence of DRHs reported in this study (245,57.9%) is substantially higher than studies conducted elsewhere, including America (16.2%), Brasil (31.6%), Denmark (10.8%), Norway(38%), Sweden (41.3%), India (17.2 %), and Malaysia (39%).[3 6 7 18-20 26 27] The high prevalence in the current study could be explained by a number of reasons: (i) The categories of DRPs causing DRHs in this study were comprehensive, whilst other studies investigated particular types of DRPs resulted DRHs such as therapeutic failure[27] and ADR [2 26 28 29]; (ii) The prospective design of this study helps to ensure the gathering all information required to accurately classify the events; (iii) Detailed histories of drug therapy obtained by clinical pharmacists might have improved detection of DRHs ; and (iv) use of the Helper's and Strand's comprehensive classification system has likely boosted the probability that all possible drug-related causes of hospitalization to be identified. In addition, the wide variability in the rate of DRHs could also be attributed to the variations in the extent of study population, inclusion criteria, study settings, participant's level of education and awareness, level of health professional expertise, methods of evaluating DRHs attributed to DRPs, study designs (prospective vs. retrospective) and the study duration. These variations are also reported by other studies.[2 10 11 28 29]

In this study, 87.8 % of DRHs were deemed to be preventable and this is in line with other international studies in which preventability of DRHs has been by far greater than fifty percent.[10-12 18 21 22 29 30] The reasons why DRHs preventability was high could be attributed to failure to taking appropriate measurements before drug related diseases were apparent. For instance, the principal categories of DRHs in our study were failure to receive drugs (130,53.5%) and untreated indication (94, 38.5%). Hence, both DRHs attributed to DRPs could be avoided by providing awareness for patients about their drugs use, applying good prescribing and dispensing practice, and providing appropriate pharmaceutical care plan.

The majority of DRHs were most commonly seen among female patients, which is concordant with a previous study.[31] However, in a study done in Saudi Arabia, DRHs were largely found in male patients.[2 22] Elderly patients developed more DRPs leading to DRHs than patients in other age groups which is also in line with other studies.[6 16 27] The main reasons could be that increased deterioration of physiologic functions and likelihood of co-morbid conditions with age. These conditions may warrant taking of multiple drugs, which ultimately serve as basis for contracting medication side effects and interactions (drug-drug or drug-food). This could possibly lead to failure to receive drugs owing to patients' non-adherence to regimens, fear of drugs side effect, unavailability and expensiveness of the drugs.

In this study, patients whose education level being elementary and below were more prone to develop DRHs than having high school education or above, which was consistent with studies done previously.[3 18] This could be related to high level education is useful to understand about appropriate medications use.

Out of a total of 245 patients with DRHs, the foremost categories of DRHs were failure to receive drugs (130,53.5%) followed by untreated indication (94,38.5%), adverse drug reactions (38,15.5%) and sub therapeutic dosage (30,12.2%). Similar findings were reported by other studies.[5 12 18 20-22 25 27 30] The major reasons for failure to receive drugs in this study were preference to cultural and religious therapies over conventional medicines, drug products were not available, cost of medications was too expensive, fear of adverse events, failure to follow-up due to Covid-19, felt better and illiteracy (near to half of patients with DRHs were illiterate). Thus, inability to recall regimens is another important reason associated with increased risk of hospitalization related to failure to receive drugs, as reported elsewhere.[3 11 21]

The second frequent category of DRHs was untreated indication (94, 38.5%) as reported in other studies.[9 22] Reasons were patients remained untreated; prophylaxis and synergistic medications were not indicated. This might be due to incorrect diagnosis; patients didn't come to health setting timely and treating physicians did not follow the management guidelines/protocols. For example, patients having moderate persistent asthma were being treated with albuterol inhalation alone. Statins have not also been prescribed for patients with atherosclerotic cardiovascular disease (ASCVDs) like peripheral arterial disease, stroke, ischemic heart disease and whose age ≥ 40 years with diabetes mellitus and high low density lipoprotein level. In addition, some compelling indication like hypertension remains untreated and subsequently results in DRHs owing to stroke and others cardiovascular diseases. Furthermore, since only cancer diagnosis and management are carried out in one of this research setting hospital, which is TASH, patients coming from different corners of the country remained untreated and/or treated with various empirical therapies that also lead to improper drug selection until they start anti-cancer drugs in TASH.

ADRs (38, 15.5%) were also commonly reported as the common classifications of DRHs, which is also mentioned with other studies.[11 19-21 29 30 32] This might be associated with numerous number of cardiac and diabetic patients in our study population and poor awareness of patients with regard to cardiac medications untoward effects such as diuretics induced electrolytes disturbance and hypoglycemic symptoms of antidiabetics. Some ADRs could be resulted from failure to follow direction for use of the medications. For example, diabetes mellitus patient who was on metformin experienced epigastric burning sensation pain and vomiting after taking metformin without meal. Overall, the plausible explanations for DRHs might be the absence of pharmaceutical care services in many health institutions including emergency wards of the study settings, which is very important for optimizing drug therapy and patient safety. There was also poor collaboration among patients, clinical pharmacists and physicians about patient's medications use process involving

medications use, their side effects, adherence issue and consequences if they will not take their medication properly. Therefore, the better opportunity for clinical pharmacists to add value in patient care roles is through ensuring medication management services according to evidence-based guidelines. In the present study, both failure to receive drugs and untreated indication were reported under the DRPs category of need additional drug therapy that resulted in DRHs, which is supported by other studies.[7 9 18]

In this study, medication classes frequently observed to cause DRHs were cardiovascular medicines, antimicrobial, antineoplastic, endocrine drugs, respiratory medicines and central nervous system drugs. Among these classes of drugs, cardiovascular drug were predominantly involved in DRHs which was in line with other studies.[3 5 6 21 25 27]Cardiovascular drugs, antidiabetics, and antiasthmatics were most commonly associated with DRHs was supported in the previous studies.[2 24 26 27] The most common drugs associated with DRHs mentioned in this study finding were furousemide, ACEIs ,insulins, oral hypoglycemic agents, warfarin, spironolactone ,aspirin and central nervous system agent and these are also implicated in several other studies.[5 7 10 21 22 24 29]The main reason might be connected with the common diseases of the study area which were heart failure, diabetes mellitus, stroke, human immunodeficiency virus and asthma.

Moreover, the most common organ system involved in DRHs was the cardiovascular system (80, 32.6%), with the most common specific disease of heart failure (55, 22.5%) which is consistent with previous studies.[6 25] Moreover, hypertension was mentioned for DRHs which was implicated in the previous study.[5 22 27]This is due to the fact that cardiovascular diseases require multiple medicine regimens and this contributed to DRPs. Among hospitalized patients attributed to endocrine systems were due to hypoglycemia, hyperglycemia and diabetic ketoacidosis, which are also cited in other studies.[22 27]It might be due to the patients poor awareness about the

hypoglycemic symptoms of anti-hypoglycemic agents , poor monitoring control and patients prefer not to take the medications.

In this study, age, educational level, length of hospital stays and presence of comorbid diseases had statistically significant correlation with the occurrence of DRHs. The findings are consistent with other studies.[18 20 30 33]

In multiple binary logistic regression analysis, patients with ≥ 65 years of age were 7.45 times more likely to be hospitalized due to drug related morbidity than non-drug related as compared to age between 14 and 24 years. This might be owing to age-related physiological changes, larger number of coexisting disease conditions, which require multiple medications and this in turn is associated with an increased risk of DRHs.

From employment factor, students were 6.3 folds high likely exposed to DRHs than non-drug related as compared to the employed. This might be explained by the nature of the disease they had which means students in this finding have majorly contracted heart failure disease secondary to chronic rheumatoid valvular heart disease. Out of a total 16 students, 9 (56.3%) of them had heart failure owing to valvular heart diseases. Consequently, it needs lifelong and multiple medications treatment and then they faced various DRPs leading hospitalizations. Moreover, participants who did not have any occupation were 3.4 times high likely to be hospitalized owing to drug related diseases than non-drug related as compared to employed.

The other factor was education level in which patients with tertiary education level were 64% less likely to be hospitalized with drug related hospitalizations as compared to participants who did not have formal education. This could be related to high level education might be useful to understand about appropriate medications use. This was supported by the studies conducted at Brasil.[3 11 18] Patients with co-morbid disease were also 2 folds high likely to be drug related hospitalized than

non-drug related as compared to patients without co morbid disease. As implicated in the previous studies,[18 30 33] co- morbidity increases the vulnerability towards DRPs. These results clearly indicate the necessity of managing DRHs in multimorbid patients.

Patients with DRHs were 2.2 times more likely to stay for > 7 days after they were hospitalized than patients with non-drug related hospitalization with estimated to < 7 days of the length of hospital stay. In terms of drug related hospital stay, the overall length of the hospital stay in the present study was 2788 days with the average length of hospital stay 11.4±9.27 days, which is longer than what has been reported in other study.[12] This was might be owing to the data in the previous study is in a single hospital and for a relatively short period of time (28 days) while in this finding, the study was carried out at three tertiary care hospitals for the periods of 60 days. Therefore, avoiding preventable DRHs is also a very cost-effective tool for health care systems and could reduce the problem of bed crisis in hospitals.

Among factors which have not demonstrated an association in multivariate analysis, polypharmacy was mentioned. This agree with what have been reported in other studies.[21 25] In contrast, polypharmacy has been reported having positive association with the occurrence of DRHs in previous studies.[3 6 11 21 22 30] This lack of significance could be resulted from variations in number of used medications and identified DRPs for causing DRHs. In this study, around two third of the patients with DRHs used from none to four drugs per patient. Accordingly, to say polypharmacy; ≥ five drugs should be concomitantly taken. Furthermore, the identified DRPs causing DRHs were failure to receive drugs and untreated indication. So, both categories reveal not taking medications and the patients might not use polypharmacy. Additionally; marital status did not illustrate significant association with DRHs.

Conclusion

The prevalence of DRHs was higher than studies conducted elsewhere among emergency ward patients in the study settings. Failure to receive drugs and untreated indication were the most frequently reported categories of DRHs. Cardiovascular drugs and drugs acting on the endocrine system have been the most frequently implicated drugs in patients with DRHs. Age, educational level, participants who did not have any occupation, presence of co-morbid condition and hospital stay have had significant association with DRHs. Hence, researches regarding DRHs should be conducted in different Ethiopian hospitals to demonstrate its impact.

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Contributors

ABB and MBD contributed to conceptualization, design, analysis and write up. MBD organized the collection of data for analysis and write up the draft manuscript. ABB and MBD supervised the collection data and overall research work including interpretation of results, reviewed and revised critically the manuscript. Both authors approved the final version to be submitted for publication.

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Competing interests

There are no conflicts of interest.

Patient consent for publication Not required

Ethics approval

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

Data availability statement

Data are accessed upon reasonable request of the corresponding author. All relevant data are within the manuscript and Supporting Information files.

Provenance and peer review

Not commissioned; externally peer reviewed.

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

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

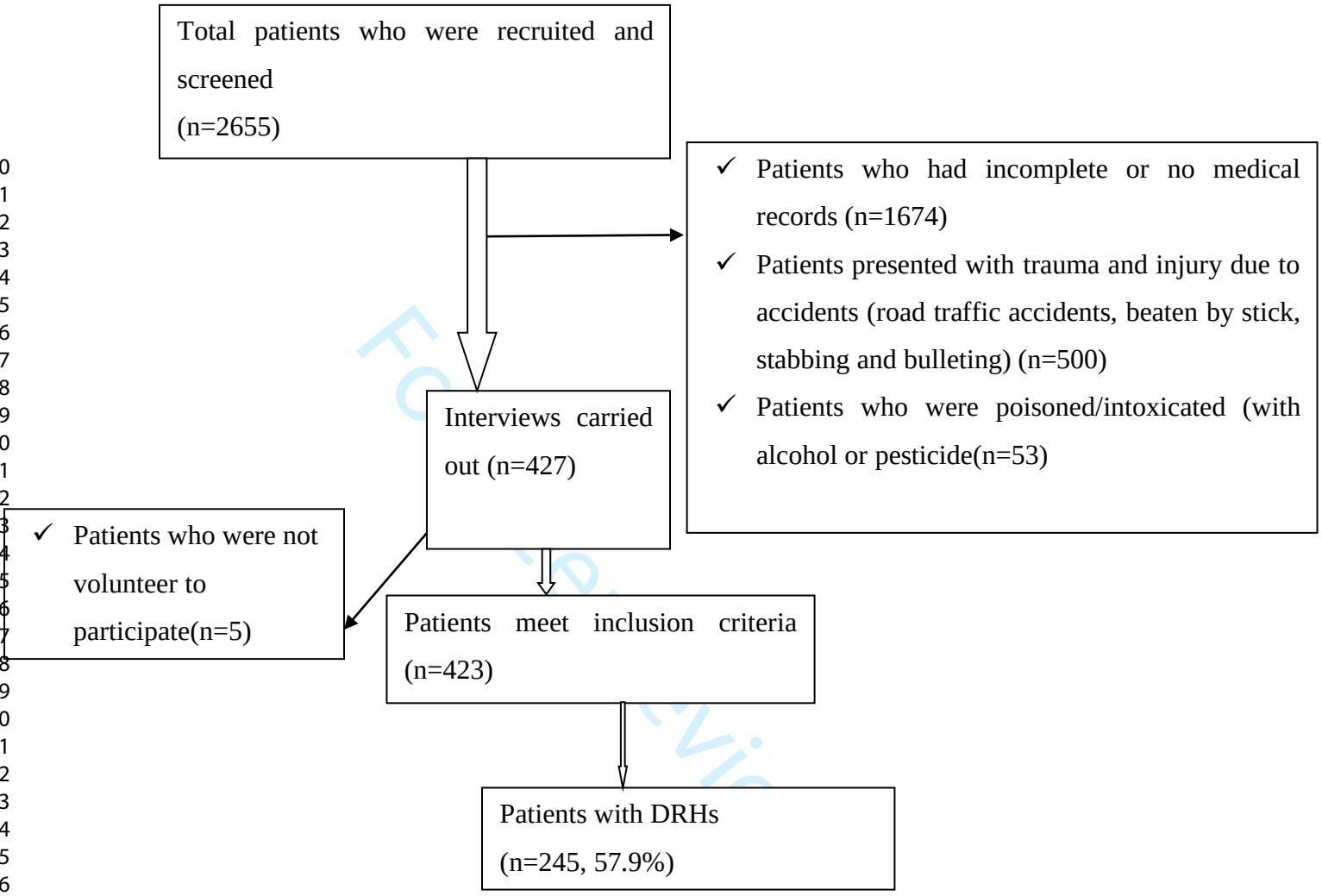

Figure 1

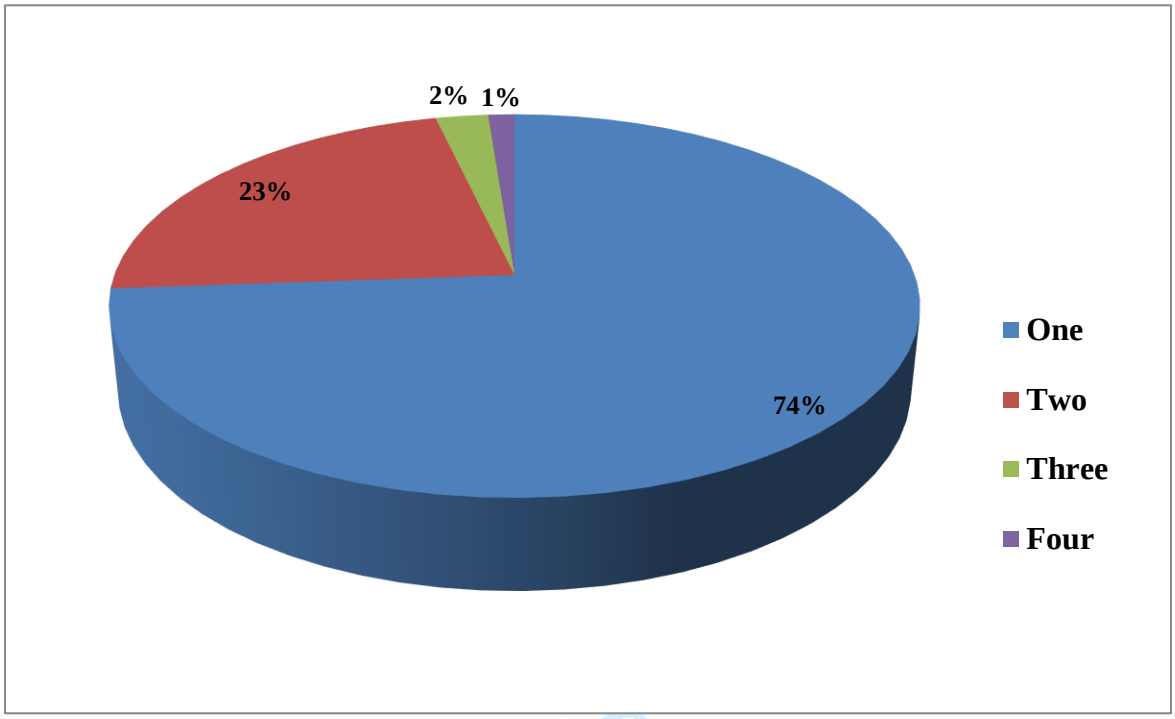

Figure 2

Editors' and Reviewers' Comments and Authors Response

Manuscript ID: bmjopen-2021-054778

Manuscript Title: Prevalence and Its Predictors of Drug-Related Hospitalizations among Patients Visited Emergency Departments of Addis Ababa City Hospitals in Ethiopia: A Multicenter Prospective Observational Study

We sincerely thank the reviewers for their significant comments and constructive suggestions which contributed to the quality of the manuscript. We have revised the manuscript as advised and changes made are highlighted in yellow at manuscript. Point-by-point response for the editor(s)' reviewers' comment is given below. We hope the revision undertaken has improved the manuscript to a level of your satisfaction and we request your editorial hand.

Editor(s)'Comments to Author (if any):

Comment1: - Please revise the 'Strengths and limitations' section of your manuscript (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The results of the study should not be summarized here.

Response 1: - We have made a correction as per comments

Comment 2: - Please complete a thorough proofread of the text and correct any spelling and grammar errors that you identify.

Response 2: - Accommodated

Reviewers' Comments to Author

Reviewer: 1 Dr. Jesus Ruiz Ramos, Hospital de la Santa CreuiSant Pau

Comment 1: - The redaction of the manuscript must be reviewed. There are multiple typographical errors in the text. The punctuation and the number of decimals used are not adequate or homogeneous.

Response 1: - We have made the correction accordingly

Comment 2: - The Tables are too extensive. The authors could include the information of the three hospitals in a single table, it does not seem necessary to differentiate the information between the different hospitals

Response 2: - Dear reviewer, from the beginning the three-hospital results merge and present in a single table.

INTRODUCTION

Comment 3: - The authors may include the following reference in the manuscript, as it shows relevant information in this field.

Response 3: - Dear reviewer thank you for your concern, we already used in reference 31.

Comment 4: Page 8, line 32. The sentence is incorrectly worded. It is not well understood why of the 2,655 enrolled patients we only assessed 426.

Response 4: First we determined a total sample size which is 423. Then put an exclusion criterion to select the patients. Here are the exclusion criteria that wrote in the text. “Patients having a medical history with completed data and ≥ 14 years old were included. Patients with incomplete or no medical records, refused to participate, presented with trauma and injuries associated with accidents (e.g. road traffic accidents, beaten by stick, stabbing and bulleting) and poisoned/intoxicated (for instance snake bite, alcohol intoxication or use of pesticide) were excluded.”. However, until to get the expected samples size, we enrolled all patients attending to the emergency department. During the study period, about 2655 were admitted to the emergency ward, and of those only 423 participants were fulfilled the inclusion criteria. One thing we want to inform you that we assessed all admitted patients not only 426. The reasons behind the higher number of patients enrollments to get the calculated sample size was due to many exclusion criteria and being in an emergency ward (high patient flow with multiple diagnoses) would be the two main reasons.

Comment 5: The revenue figure for DRPs is certainly misleading. Many patients, mainly surgical, were excluded from the study. The authors must make it clear in the abstract are during the text that this is a study in medical patients (Is not a real prevalence or all patients attended in the hospital). This concept should also be repeated in the discussion

Response 5: Dear reviewer, in our study setting almost all patients (medical case, surgical case, and others) were attending to the emergency ward as a triage then if the patients were candite for further admission, they went to surgical and medical wards. However, other cold cases or

ambulated patients directly go to the various clinics for follow-up, in case some patients still there will be a probability of admission to different wards. Therefore, we missed those patients who came from other than an emergency ward, because of this we put a limitation on this study next to an abstract section under the title of 'Strength and limitations of the study and also in the title of 'limitation of the study.

Comment 6: Consider change "chemotherpautic drugs" for "chemotherapy drugs" or "antineoplastic drugs" (ATC / WHO definition)

Response 6: Dear reviewer, as per the comments we put the name of 'antineoplastic drugs' for list of anticancer drugs and 'antimicrobial drugs' for the lists that comprise antibiotics, antifungals, antiprotozoals, and antivirals.

"Antimicrobial" is a general term that refers to a group of drugs that includes antibiotics, antifungals, antiprotozoals, and antivirals.

Comment 7: Page 23, line 23. Regarding risk factors implicated in DRH admission, the approach used by the authors doesn't seem correct. The authors found differences between patients hospitalized by DRPs and for other causes, buy these variables cannot be considered as risk factors. In order to study risk factors, a study including patients that are not hospitalized and patients hospitalized is needed. In very opinion, the authors should change the concept "risk factors" for differences between patients hospitalized by DRPs or others causes.

Response 7: Dear reviewer, as you have seen the exclusion criteria, we recruited only patients who were taking drugs upon admission to the emergency ward. Then, we evaluated the patients by multi-disciplinary team whether they have drug-related problems or not. Here again, we classified those patients who have DRPs that lead to DRH or not to determine the possible risk factors (these risk factors putting as independent variables after reviewing various literatus that cause DRH). One thing to remind you that the other causes of hospitalization without taking medication upon admission were excluded from the beginning. OR

Moreover, Factors associated with drug-related hospitalization were determined in accordance with variables that were described as independent variables and evidence that was extracted from the literature. Accordingly, we identified that which factors were having a significant association with hospitalization owing to drugs-related.

Comment 8: Page 23, line 28-60. The paragraph must be redrafted. It is not necessary to explain what an OR means (it is known by the readers; it is enough to indicate the OR value

Response 8: Accommodated

Comment 9: On page 16, line 23 there is a citation not properly included. Also, unify the names of the authors in the bibliography (Some names are in Capital letters)

Response 9: This paragraph comprised the findings of the present study that didn't require the insertion of references. Regards to the bibliography we have made a correction.

Comment 10: Discussion: Page 35 line 42. Please, define EW

Response10: We have made the correction as per the comment. We used the word 'emergency department' (ED) in the whole document for consistency

Comment 11: Conclusion: Page 35, line 55: Consider modifying the expression. "Relatively High" for "Higher than in studies published in other countries." It is undoubtedly the most relevant conclusion of this study

Response11 Accommodated.

Comment 12. Page 36, LINE 14-27: Consider deleting lines 14 to 26. These sentences are statements that do not correspond to the results of the study.

Response12 Accommodated

Reviewer 2: General Comments to the Author:

Dr. Aisha Vadhariya, Eli Lilly and Company

Comment 1: - My first comment is about the general flow, grammar and interpretability of the manuscript. I suggest revision in the writing and review of the grammar and review the content in tables/ figures. There seem to be missing values in the tables.

Response 1: - We have a correction as per the comment.

Comment 2: - My second comment is regarding the methods. There is very little emphasis on the actual content of the data collection sheet which determines the main outcome of the study i.e. DRH. There should be transparency for the readers to understand the definition used to categorize a certain case as a DRH vs not.

Response 2: - Accommodated.

Comment 3: - The results tables have some categorizations that need to be collapsed to be made more meaningful. I suggest limiting the content of the tables to the one's pertinent to the study. There is point-by-point discussion for each major finding however, the assumptions/extrapolations

from the results may not be valid/accurate. This is a point in time data collection and causality should not be so easily inferred. This is a major concern I have from this study.

Response 3: - Dear review, thank you for your comment. One thing we want to inform you that most of our results emanated from the data collecting tools. The data collection tools were prepared after extensively revising many published articles to capture the important variables that could be affected/ determined DRHs across the globe. And also, we tried to contextualize based on our setting.

Reviewer 2: Specific Comments to the Authors

Comment 1: Pg. 1 line 56 (Abstract): …. from failure to receive drugs followed by untreated indications (awkward –start a new sentence. Also (and independent of phrasing), these two categories would appear to overlap a good deal (if not be exactly the same. How are they different?).

Response 1: We have made a correction as follows. The cause for hospitalization for more than half (130, 53%) of them was failure to receive drugs and 37.85 (94) patients were categorized as untreated indications.

For further clarification, even though, the two terms it seems similar, however, they are quite different, you can see the difference here is below.

Failure to receive drugs: diseases that resulted from not receiving a drug due to unavailability or unaffordability drugs, patients no need to take drugs or stop taking medications upon they felt better e.t.c. In failure to receive drugs, the patients have information about the drugs that are being taken.

Untreated indication: medical condition needing new drug therapy, or preventive therapy is needed to reduce the risk of developing a new condition, or a medical condition requires combination therapy for better efficacy (STRAND, 1990). Here, patients did not know the drugs they should take.

Comment 2: Pg. 4 lines 18-23: In the globe, medications use has becoming increased because of the presence of large number of diseases (which are treatable by such medication use??), and thus contribute ….

Response2: We have been accommodated in the revised version.

Comment 3: Pg. 4 line 49: Over the past decades, DRHs have been stated as prevailing (??).

Response 3: Dear review thank you for your comment. We have made a correction as per the comments and also cited accordingly by inserted reference.

Comment 4: Pg. 4 lines 49-54: …..17 million emergency department (ED) visits and 8.7 hospital admissions accounted from DRPs annually (probably trying to say: DRPs accounted for 17 million ED visits and 8.7 hospitalizations annually).

Response 4: We rewrite as per the comment.

Comment 5: Pg. 5 lines 25-27: …..financial difficulties whilst if there was no reasonable actions to prevent DRPs which is termed as non-preventable (difficult phrasing - consider starting a new sentence).

Response 5: Accommodated

Comment 6: Pg. 6 lines 48-51: Patients played the central role in this study in determining the level of medication use, adherence, and medical history (don't know what is really meant here, but it is probably different from what is stated).

Response 6: Dear reviewer thank you for your comment. The point what we want to inform you/the reader/ that during the data collection of periods, patients alone or patients with the help of their family were actively participated in determining the medication use, level of adherence, and medical history. For the sake of clarification, I rewrite the statement with slight modification. 'Patients who participated actively in this study determine the medication use, level of adherence and medical history.

Comment 7: Pg. 8 lines 53-57: ….. data abstraction formats (?) were reviewed and cheeked (sp!) for their completeness every day to assure its quality. Urgent correction was made, if any errors were identified.

Response 7: We modified the statement as follows. 'The data collection process was supervised, and the information gathered via data abstraction formats were reviewed and checked for their completeness every day to ensure its quality. An urgent correction was made, if any errors were identified'

Comment 8: Pg. 16 lines 11-13: ……245 patients, representing 1.31 DRPs per patient, since 55 (22.4%) patients presented two DRPs (figure 2). (Just drop this last clause. Misleading, as only '2' is mentioned when '2','3', and '4' were observed).

Response 8: Accommodated

Comment 9: Pg. 18 lines 40-47: ….nearly one third ……which was stroke (26,10.6%) (Run-on sentence rephrase to split into two sentences).

Response 9: We shortened the statement to accommodate reviewer 2 comment

Comment 10: Pg. 21 lines 6-8: A total of 497drugs ……involved in DRHs. (Unusual wording, including use of 'pertained to' and 'entails', change in tenses, change from passive to active verb. Consider rephrasing).

Response 10: Accommodated

Comment11: Inclusion/exclusion criteria (pg 7): Explain more in the text how your original group of 2,655 eligible patients led to 423 study participants (as described in top of figure 1).

Response 11: First we determined a total sample size which is 423. Then put an exclusion criterion to select the patients. Here are the exclusion criteria that wrote in the text. "Patients who had incomplete or no medical records, patients who refused to participate, patients presented with trauma and injuries associated with accidents (e.g. road traffic accidents, beaten by stick, stabbing and bulleting) and who was poisoned/intoxicated (for instance snake bite, alcohol intoxication or use of pesticide) were excluded". However, until to get the expected samples size, we enrolled all patients attending the emergency department. During the study period, about 2655 were admitted to the emergency ward, and of those only 423 participants were fulfilled the inclusion criteria. One thing we want to inform you that we assessed all admitted patients not only 426. The reasons behind the higher number of patients enrollments to get the calculated sample size was due to many exclusion criteria and being an emergency ward (high patient flow with multiple diagnoses) would be the two main reasons.

During data collection periods, about 2655 patients were being admitted and assessed whether they fulfilled the inclusion criteria or not. Of those, 423 participants only fulfilled the inclusion criteria.

Comment 12: Analyses (pg 9): The descriptors 'univariate' and 'multiple binary logistic regressions' are not always correctly used. The models you referred to as multiple binary logistic regressions are really multivariate logistic regressions. Table 1 does provide real univariates (albeit overall and stratified by DPH status), but when you go on to test whether percentages are different between DPH and non-DPH groups, then you are performing bivariate (two-variable) analyses. Thus, your sentence should read '….variables whose p-values<.2 in the bivariate analyses were included in the multivariate logistic regressions'. In line with this, it would make sense to indicate

in Table 1 all the factors which were significant (or highly significant) in these binary analyses. This can be done with asterisks (* for significant or ** for highly significant). Table 5 should only show the AOR (95% CI) and p-values from the multivariate logistic regressions. The n (%) results just repeat values in Table 1. If you really need to present CORs, they should be in Table 1 as well (but asterisks for significant bivariate associations are probably sufficient).

Response12: We have made a correction as pe the comments.

Comment 13: Analysis Variables:

-The logistic models should not include the length of stay variable (greater than 7 days). This variable becomes known after admission, not at the start, and thus is really an outcome of DPH, not a predictor.

-Change the descriptor 'Causes' in the table header. Cross-sectional, observational models cannot demonstrate causality.

-relabel 'Employed' as an employment status (consider instead 'wage or salaried worker'). The term

Employed could be interpreted more broadly than intended (and thus overlap with merchant, day laborer, and farmer).

- I approve that only indicator for polypharmacy (5+) is in the regression model, but for consistency (and

to be less confusing) consider using categories 0, 1, 2, 3-4, and polypharmacy for number of drugs in

Table 1. Don't need 3-5, more than 5, and polypharmacy as separate indicators in this table.

Response 13: Dear reviewer, the intention is to demonstrate that patients with DRHs were 2.2 times more likely to stay for > 7 days after they were hospitalized than patients with non-drug related hospitalization with an estimated to < 7 days of the length of hospital stay. Moreover, "Length of stay" can be a predictor or outcome of DRHs. Once the patients were admitted to the emergency ward and who fulfilled the inclusion criteria, we followed those patients until to discharge from the hospital. At that moment some patients might be developed drug-related problems rendering to DRHs or not. During follow up those admitted patients to the emergency ward who fulfilled the inclusion criteria at the beginning didn't have any drug-related problems, however, due to staying a longer period of time (patients might be exposed to hospital-acquired infection which leads to receiving multiple medications), they develop drug-related problems that

would result in DRHs outcomes. Patients who had DRHs stayed more time in the emergency ward than patients with non-DRHs.

We have made a correction by considering using categories 0, 1, 2, 3-4 of the number of medications taken per patient. About polypharmacy, I understand your concern, however, according to standard definition for those patients who took more than or equal to five drugs considered as polypharmacy. "Yes" or "No" polypharmacy classification is useful to interpret its association with the clinical outcomes.

We have accommodated all the remaining comments in the text.

Comment 14: Shortening some Tables (pgs. 17-23): Tables 2, 3, and 4 are probably too detailed to include in the paper. Consider shortening these tables by using only the broader categories - with a note that further breakdowns are available from the author upon request. Also, Table 1 is included twice in the paper (this could be an editing issue at the journal's end).

Response 14: Dear reviewer as per the comment, we shortened table 3. Whereas the table 2 & 4 we believed that the main objective of this research work. So, the findings presented in the broader categories in Tables 2 & 4 will have paramount importance for the readers.

Comment 15: Comparison of DRH rates (pg. 26): Some of the DRH rates from other countries (other referenced studies) are so different, that they can't possibly be measuring the same thing. Consider comparing current results with a smaller set of previous ones, dropping those which are not nearly as comprehensive (e.g., America, Denmark, Greece, India).

Response15: A study done in India assessed the prevalence of DRH in a similar way in the present study. On the other hand, studies conducted in America and Denmark also assessed DRPs and subsequently determine the prevalence of DRH (the methods are somehow different from our study).In effect, all of the studies determined the prevalence of DRHs in one or the another way. That way we compared the findings of this study with those lists of studies.

Response to Reviewer's 3 comments

Page 3 line 34

Comment 1: Since the study was based of patients only in the emergency ward, did it capture patients through other channels? IF not, then the number identified cannot be true incidence

Response 1: Dear reviewer, this study was carried out in the emergency ward of three hospitals, patients who required admission through various channels such as ambulatory and different specialty clinics were sent back again to the emergency department triage before admission to various wards. Therefore, in our study settings, the admission procedure is less likely for patients admitted without passing the triage of emergency wards. Being a sufficient samples size and multicenter study, this study can be showing us the true incidence.

Comment 2: Page 6 line 14, I am not sure how the information about the year they are founded has relevance to the methods.

Response 2: We have made a correction as per the comments/ deleted the founding years/

Comment 3: Page 7 line 11, rigorous evaluation is a subjective term. What was extracted from the literature? Need more clarity on the development of the questionnaires/tool

Response 3: We change the word 'rigorously' by 'carefully'. However, the statement tales about the instrument I should go to the 'Data Collection' section. For your information: "A structured questionnaire was developed from carefully evaluated published articles in the literature. For instance, categories of DRPs that leads to hospitalization and factors having association with DRH (e.g. socio-demographic and clinical characteristics) were extracted from literatures".

Comment 4: ED vs EW?

Response 4: We use those terms interchangeably in various guidelines/ protocols and published articles. ED: Emergency department; or EW: Emergency ward. However, to make consistency afterward we used the Emergency department (ED) in this manuscript.

Page 7 line 16

Comment 5: Please mention if there was any ethics approval required for the study

Response 5: we have made a correction as per the comment. However, the content move to the 'Ethical Approval' section to end of Manuscript before the "Reference section' . For your information see the following paragraph.

Patients' names were not used rather codes to maintain the confidentiality of the information throughout the study period. Verbal consent from patients was obtained after the provision of information regarding the purpose of the study and its risk for the interviewee which could be time to be spent during the interview (maximum of 30 minutes). Patients were told the reasons for being selected to be included in the study and assured that waning participation would not have any influence on the right to get treatment. Patients were also told about their rights to withdraw from

the study at any time. Moreover, as per BMJ open journal outline, we mentioned Ethical Approval on page 38 lines 19-25. “Ethics approval prior to study initiation, letter of ethical approval (Ref No; ERB/SOP/172/08/2020) was obtained from the ethical review committee, School of Pharmacy, College of Health Sciences, Addis Ababa University”.

Comment 6: Page7 line 22 edit: 'who refused to participate'

Response 6: Accommodated

Comment 7: Page 7 line 47, why has P been selected as 0.5?

Response 7: Since there was no study done on DRHs in Ethiopia, the sample size was estimated using the general formula for single population proportion and P has been taken as 0.5 to simply increase the sample size.

Comment 8: Page 7 line 52, can the authors please clarify more what this 10% contingency is for?

Response 8: It is significant to compensate participants who were refusing to participate and thereby sufficient sample size was found.

Comment 9: Page 8 line 10, is this one pharmacist per hospital?

Response 9: Yes, all three pharmacists were independently collecting the data from respective hospitals, but they have been discussing and deciding together on hospitalization attributed to drugs-related problems. This is paramount to minimize self-selection bias.

Comment 9: Page 8 line 18, were there missing values? Were any imputation techniques used?

Response 9: As it is expressed under inclusion and exclusion criteria, patients who had incomplete or no medical records were excluded because of their missing values.

Comment 10: Page 8 line 19. More information about the questionnaire should be added and the variables that were collected to provide transparency to the readers about how was a determination made whether a hospitalization was drug-related.

The definitions from literature are mentioned in the background, but the definition that was used for this particular study should be provided.

Response 10: Data were collected by three pharmacists having Master of Science degrees in Clinical Pharmacy. They had basic knowledge and skill in pharmaceutical care services and also received training on how to obtain data from patients' medication charts and approach the patients and health care professionals. Updated Ethiopian Standard Treatment Guidelines for Hospitals, third edition, 2014, Ethiopian Antiretroviral Therapy and Tuberculosis Guidelines, Cancer Treatment Protocols prepared by TASH Oncologists, Pharmacotherapy textbooks, Medscape, UpToDate were used as a guide for diseases management, and also Micromedex online database was used to check the drug interaction. Furthermore, updated guidelines released from American Cardiology Center, American Heart Association, European Cardiology Society, American Diabetic Association were used as a guide to treat different diseases. Clinical pharmacists along with physicians were determined subtherapeutic and supratherapeutic dosage outcomes using the medical charts, laboratory tests, clinical outcomes, medication dose, and frequency. Participants hospitalized attributed to failure to receive drugs were decided via using physician's recording documentation, clinical pharmacists' knowledge, and patients reporting evidence. And also, untreated indications and improper drug selection were being evaluated and interpreted by using treatment guidelines. For instance, if patients presented with cardiac diseases which were untreated or improperly treated identified using the American Heart Association guidelines, and UpToDate latest version. To minimize bias, the three pharmacists at each hospital were evaluated independently following the identified DRPs rendered hospitalizations. Consequently, they were meeting and discussing their judgment to DRPs resulting DRHs. Accordingly, DRPs rendering DRHs were determined after they have been reaching on concord. Moreover, Physicians and residents were involved in interpreting DRPs causing hospitalizations. Once DRPs resulting DRHs were identified, they were recorded and classified using DRPs registration format according to Helper's and Strand's classification.

Comment 11: Page 9 line14. Is there a need for univariate logistic regression? The results are going to be unadjusted for confounders anyway with this technique.

Response 11: Yes, I agreed on it. Certainly; univariate logistic regression does not limit/control confounders. However, in this study, we tried to control the confounding factors by doing further analysis using multiple logistic regression.

Comment 12: Need to explain what variables were adjusted for in multiple binary regressions

Response 12: As it is already mentioned, Variables with P-values < 0.2 in the binary logistic regression analysis were included in the multiple binary logistic regressions to control the effect of confounders.

We put asterisks for those variables having significant bivariate associations in Table 1. For further information see the below paragraph.

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

Comment 12: Suggest the use of chi-square tests and t-tests to capture differences in baseline demographic and clinical characteristics between these two groups.

Response 12: We have done by using chi square tests and t-tests.

Comment 13: Page 9 line 54 and 57. Is the age missing here?

Response 13: Accommodated

Comment 14: Page 10 line 46. Suggest breaking employment into 2-3 meaningful groups. Collapse these categories into small groups.

Response 14: We have done as per the comment.

Comment 15: Page 14 line 13. Typo

Response 15: Accommodated

Comment 16: Page 14 line 24. Would recommend collapsing the two physical activity variables into one category- any physical activity vs not

Response 16: We have made a correction as per the comments.

Comment 17: Page 14 line 41. Some of these variables are confusing and should be explained better in the methods section. The methods section does not have sufficient information about the questionnaire. What does other drugs indicate?

Response 17: We rewrite the statement; other drugs indicate that traditional home remedies (herbals) were being used.

Comment 18: Is there some missing information in these tables?

Response18: No missing information. This is similar to what is corrected in comment 13.

The number of medications taken per patient serves as an umbrella for both continuous and categorical variables.

Comment 19: Page 15 line 31. Missing information here as well

Response 19: We deleted the content due to Reviewer 1 raised concerns about its importance

Comment 20: Page 16 line 23. Referencing error

Response 20: This wasn't a reference error, by default computer-related typographic error. We wrote the word 'Table 2' instead of inserting the reference.

Comment 21: Page 16 line 38. Untreated indication would mean that a condition exists that receives no therapy at all. Improper management i.e. need of a potentiating drug may not fall into lack of treatment

Response 21:Untreated indication includes medical condition needing new drug therapy, or preventive therapy is needed to reduce the risk of developing a condition, or a medical condition requires combination therapy for better efficacy (STRAND, 1990).

Comment 22: Page 18 line 10 Does this categorization refer to patients not using drugs as instructed i.e. adherence and compliance issues?

Response 22: Failure to receive drugs encompasses not only using drugs as directed. And also diseases that resulted from not receiving a drug for unavailability or unaffordability of drugs. For more, you can see causes of failure to receive drugs with their respective proportions as you mentioned in comment 22.

Comment 23: Page 19 line 10. Can you indicate in the table or text that the DRH was related to this particular disease. E.g. lack of treatment with hypertensives of hypertension was the reason for the hospitalization? This part is not clear in the manuscript

Response 23: Dear reviewer, in addition to your comment, Reviewer 2 also raised concern about the size of the Tables. So, we made a correction by congesting Table 2 in short form by listing only the 'major classification of drugs.

Comment 24: Page 24 line 24. It is incorrect to list these as causes of hospitalization - these as mentioned above are merely predictors. This study is not determined to establish causality

Response 24: We have made a correction as per the comments.

Comment 25: Page 25 line 27. Same comment as above to collapse employment and education categories

Response 25: Accommodated.

Comment 26: This statement is confusing. The proportion of females in the DRH and non-DRH group is very similar. What is the basis of this?

Response 26: Among the total of 216 included female patients, 126 of them were hospitalized due to drugs-related as it is specified in Table 1 .in percent it comprises 51.4%.

Comment 27; Page 31 line 37. Examples are helpful

Response 27: Dear reviewer, we already included the example next to this statement.

Comment 28: Page 34 line 5&7. This finding surprises me because students tend to be younger in age and CV diseases increase with increasing age.

Response 28: Even though it is known that as age increased cardiovascular diseases prevalence is also increased, individuals in younger age may encounter significant cardiovascular diseases attributed to rheumatic heart disease/ valvular heart diseases. As we know the rheumatic heart disease mainly affected the younger age group of the population and is common in developing nations like in Ethiopia. In sub-Saharan Africa, studies from multiple countries report that approximately 0.5–3% of school-age children have echocardiographic signs of definite or borderline disease according to World Heart Federation (WHF) criteria.

Comment 29: Was a subgroup analysis performed in the student group to make this statement?

Response 29: Yes, it was performed. Of the total of 16 students, 9 (56.3%) of them had heart failure owing to valvular heart diseases.

Comment 30: Page 34-line 42. The outcome of the model is DRH - so the assumption is the reason for H was drug-related. This says patients developed DRH after staying in the hospital which does not align conceptually.

Response 30: Dear reviewer, the intention is to demonstrate that patients with DRHs were 2.2 times more likely to stay for > 7 days after they were hospitalized than patients with non-drug related hospitalization with an estimated to < 7 days of the length of hospital stay.

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Prevalence and Predictors of Drug-Related Hospitalizations among Patients Visiting Emergency Departments of Addis Ababa City Hospitals in Ethiopia: A Multicenter Prospective Observational Study

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ABSTRACT

Objectives: This study aimed to determine the prevalence, categories, and predictors of drug-related hospitalizations (DRHs) among patients visiting emergency departments of Addis Ababa city hospitals, Ethiopia.

Design: A multicenter prospective observational study was conducted through patients interview and chart review.

Settings: The study was undertaken in three tertiary care hospitals, Addis Ababa, Ethiopia.

Participants: A total of 423 patients fulfilling the inclusion criteria were included.

Outcome measures: Prevalence and preventability of DRHs, categories of drug-related problems causing DRHs, medications, and diseases involved in DRHs, and factors significantly associated with DRHs.

Result: More than half of the patients (216, 51.1%) were females. The mean age (SD) was 47.50 (±17.21) years. The mean length of hospital stay (SD) was 10.29(±8.99) days. Nearly, 60% (249) of them were hospitalized due to drug-related problems, of which 87.8% were preventable. The cause for hospitalization for more than half (130, 53%) of them was a failure to receive drugs, and 37.85 (94) patients were categorized as untreated indications. Age ≥ 65 years (Adjusted Odds Ratio [AOR]=7.451,95%CI: 1.889-29.397), tertiary educational level (AOR=0.360, 95%CI: 0.141-

0.923), participants who did not have any occupation (AOR=3.409, 95%CI: 1.120-10.374) and presence of co-morbid conditions (AOR=2.004, 95%CI: 1.095-3.668) were predictors of DRHs.

Conclusion: Nearly 90% of DRHs were deemed to be preventable in the study settings. Older age, lower educational level, unemployment, and presence of the co-morbid condition in hospital as an inpatient were predictors of DRHs**.**

Strength and limitations of the study

- The strength of this study is the study design which is a prospective observational study.
- This is a multicenter study with sufficient sample size, increasing representativeness the findings.
- The main limitation of this study is lack of standardized procedures for immediate recording and reporting of DRHs.
- Patients who visited other than the emergency ward were excluded from participation can also be considered as a limitation of the study.

INTRODUCTION

Though drugs can be ordered for the intention of achieving desired health outcomes that improve patients quality of life, symptoms and signs of diseases causing drug related hospitalizations (DRHs) as a result of drug related problems (DRPs) could be apparent.[1-3] DRP is defined according to Helper and strand as 'an undesired event or circumstance due to drug therapy that actually or potentially interferes with desired health outcomes'.[4]

Medication's use has been increasing across the globe due to the presence of large number of treatable diseases and this has contributed to production of more advanced medications by the pharmaceutical industries. Therefore, advances in drug therapies could lead to an apparent increase in the incidence of DRPs, which in turn lead to hospitalization[5]. Hospitalization can be defined as drug related if it is straightforwardly linked to one of the eight predefined Helper's and Strand's classifications of DRPs: adverse drug reaction (ADR), drug interaction, improper drug selection, untreated indication, sub-therapeutic dosage, supra-therapeutic dosage, failure to receive drugs, and drug use without indication.[6-12] Those DRPs can arise when a medicine is prescribed aptly and used correctly (e.g., ADR), due to errors involving prescribing (including inappropriate or over-treatment, and failure to prescribe the indicated treatment or under-treatment), dispensing, administering, reconciling, or monitoring of medicines as well as from poor patient adherence.[2 13 14] According to the World Health Organization (WHO), an ADR is any harmful, undesired and inadvertent drug effect that occurs at doses used in human for therapy, diagnosis or prophylaxis.[15]

Over the past decades, DRHs have been considered as wide spreading[16]. In the United States, DRPs accounted for 17 million emergency department (ED) visits and 8.7 hospitalizations annually.[17] It increases morbidity and mortality rates, health care cost, decreases income and household productivity and reduced quality of life.[2 18 19]

Studies carried out in different areas of the globe estimated the extent of DRHs to be between 16% to 41.3%. Of these, 50% to 95% were preventable. Supratherapeutic dosage (10.3%-12.7%), non-compliance (10.6%-65.8%), ADRs (10.7%-45.5%) and untreated indications (10.7-13.3%) were frequently identified as the causes of DRHs.[6 9 18 20-22]

DRPs resulting DRHs were defined as preventable if the patient failed to take a drug that is known to reduce or prevent symptoms according to the prescribed directions, took a drug for which a patient had a known allergy, drug treatment was obviously improper, dosage differed from accepted recommendations, took a drug that was not indicated, and if there was a failure to monitor by a physician at reasonable time intervals due to financial difficulty. If there was, however, no reasonable actions to prevent DRPs, it is then termed as non-preventable.[20 23]

In many studies, patients with DRHs had mainly cardiovascular diseases and diabetes, suggesting that cardiovascular and hypoglycemic medications were involved in DRHs.[6 10 11 18 20 21 24 25] Previous studies also identified polypharmacy, advanced age and comorbid conditions as factors that favor the occurrence of DRHs.[3 6 20 21]

It is thus important to determine DRHs prevalence to improve treatment outcomes and prevent unnecessary admissions. To the best of our knowledge, there are no studies conducted about DRHs in Ethiopia. The present study therefore aimed to determine the prevalence, categories and predictors of DRHs among patients admitted to an ED of three selected hospitals in Addis Ababa, the capital of Ethiopia.

METHODS

Study Settings

The study was carried out in the ED of Tikur Anbessa Specialized Hospital (TASH), Zewditu Memorial Hospital (ZMH), and Yekatit 12 Hospital Medical College (Y12HMC), Addis Ababa, Ethiopia. TASH has 700 beds and it is a tertiary care teaching hospital affiliated with Addis Ababa University. In TASH, outpatient, inpatient, and emergency services are delivered. The ED provides services for about 13,920 patients per year. Y12HMC is also a tertiary carry level referral and teaching hospital that provides both inpatient and outpatient treatment for a large number of people coming from Addis Ababa as well as other places of the country. The hospital has a total of three ED rooms. The adult medical ED is collocated with adult surgical ED. It serves around 10,560 patients per year. The third hospital is ZMH, which is one of the teaching and general referral hospitals in Ethiopia and the ED serves about 10,560 patients per year.

Patient involvement

Patients did not participate in the initial conception and design of the study. However, based on the participating patients' comments during the pretest (5% of the sample size), we made a correction on the patient approach and timing for an interview at ED during data collection. Patients who participated actively in this study determined the medication use, level of adherence, and medical history.

Study design and population

A prospective observational study design was used to collect data from August to September, 2020. All patients admitted to the ED of the three selected hospitals during the study period and fulfilled the inclusion criteria were included.

Inclusion and exclusion criteria

Patients having a medical history with completed data and ≥ 14 years old were included. Patients with incomplete or no medical records, refused to participate, presented with trauma and injuries associated with accidents (e.g. road traffic accidents, beaten by stick, stabbing and bulleting) and poisoned/intoxicated (for instance snake bite, alcohol intoxication or use of pesticide) were excluded. During data collection periods, about 2655 patients were being admitted to the ED, out of which 423 participants fulfilled the inclusion criteria

Sample size determination and techniques

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

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

(Hence; n = required sample size, Zα/2 = critical value for normal distribution at 95% confidence interval, which equals 1.96 (*Z* value at alpha = 0.05), P = Proportion of DRH =0.5, d = margin of error of 5%=0.05. The calculated sample size using this formula was 384. Adding 10% contingency (for non-response rate) to compensate participants who could refuse to participate, brought the final sample size to 423. The sample size was distributed to the three hospitals based on the patient load of hospital's ED per annum as mentioned in the Study settings. Accordingly, 169 participants were included from TASH, 127 participants from ZMH and 127 participants from Y12MHC.

Data collection procedures

A structured questionnaire was developed from carefully evaluated published articles in the literature. For instance, categories of DRPs that leads to hospitalization and factors having association with DRH (e.g. socio-demographic and clinical characteristics) were extracted from

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

Data were collected by three pharmacists having Master of Science degrees in Clinical Pharmacy. They had basic knowledge and skill in pharmaceutical care services and also received training on how to obtain data from patients' medication charts and approach the patients and health care professionals. Updated Ethiopian Standard Treatment Guidelines for Hospitals, third edition, 2014, Ethiopian Antiretroviral Therapy and Tuberculosis Guidelines, Cancer Treatment Protocols prepared by TASH Oncologists, Pharmacotherapy textbooks, Medscape, UpToDate were used as a guide for diseases management. Micromedex online database was used to check drug interactions. Furthermore, updated guidelines released from American Cardiology Center, American Heart Association, European Cardiology Society, American Diabetic Association were used as a guide to treat different diseases. Clinical pharmacists along with physicians determined subtherapeutic and supratherapeutic dosage outcomes using medical charts, laboratory tests, clinical outcomes, medication dose and frequency. Participant's hospitalization attributed to failure to receive drugs was decided using physician's recording documentation, clinical pharmacists' knowledge and patients reporting evidence. Untreated indications and improper drug

selection were evaluated and interpreted using treatment guidelines. For instance, if patients presented with untreated or improperly treated cardiac diseases, treatment was initiated and optimized using the American Heart Association guidelines, and UpToDate latest version. To minimize bias, the three pharmacists at each hospital independently evaluated the identified DRPs resulted hospitalizations. Decision was then reached by reaching consensus after a series of meetings and discussions as well consultations with physicians and residents. Once DRPs resulting DRHs were identified, they were recorded and classified using DRPs registration format according to Helper's and Strand's classification.

Data collection management

Pretest was performed on 5% patients in TASH prior to the actual data collection period and amendment was made accordingly. The data collection process was supervised, and the information gathered via data abstraction formats were reviewed and cheeked for their completeness every day to ensure quality. Urgent correction was made, if any errors were identified.

Data analysis

The data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 26. Mean and standard deviation for continuous variables and frequency and percentage for categorical variables were computed by using descriptive statistics in SPSS to summarize socio-demographic and relevant clinical characteristics of the study participants. Tables and charts were used to present the results. Furthermore, univariate and multiple binary logistic regressions were performed to analyze factors that predict DRHs. Variables with p-values < 0.2 in the binary univariate analysis were included in the multiple binary logistic regressions to control the effect of confounders. The level of significance was set at p–value ≤ 0.05 and results were reported as odds ratios (OR) with 95% confidence intervals.

RESULTS

Socio-demographic and clinical characteristics

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

Socio-demographic and clinical characteristics of the participants is depicted in Table 1. More than half of the participants (216, 51.1%) were females. The mean (SD) age of the participants was 47.5 (±17.21) years and nearly two third (275, 65%) were ≥ 40 years of age. More than 70 % (301, 71.1%) of the total participants' level of education was below secondary school. Nearly three-quarter of them (304, 71.9%) resided in Addis Ababa city. Out of the total study participants, 58% (245) of them were taking ≥3 and 30% (127) ≥ five drugs prior to admission, which is termed as polypharmacy. Above half of the participants (213, 50.4%) had co-morbid diseases, including hypertension (108, 22.5%), cardiac diseases (59, 13.5%) and diabetes mellitus (53, 12.5%). The mean (SD) length of hospital stay was 10.28±8.99 days and ranges from 2 to 96 days.

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

Variables	[1]DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Gender			
Male	119(48.6)	88(49.4)	207(48.9)
Female	126(51.4)	90(50.6)	216(51.1)
Age* (in years)			
Mean± SD	48.23±17.85	46.5±16.3	47.5±17.2
14 - 24	24(9.8)	14(7.9)	38(8.98)
25- 39	51(20.8)	59(33.1)	110(26)
40 - 64	100(40.8)	74(41.6)	174(41.1)
>64	70(28.6)	31(17.4)	101(23.9)
Marital status*			
Single	64(26.1)	34(19.1)	98(23.2)
Married	129(48.6)	105(59)	234(55.3)
widowed	20(8.2)	9(5.1)	29(6.7)
Divorced	42(17.1)	31(16.9)	73(17.3)
Education level*			
No formal education	116(47.3)	72(40.4)	188(44.4)
Elementary	66(26.9)	47(26.4)	113(26.7)
Secondary	31(12.7)	35(19.7)	66(15.6)
Tertiary	32(13.1)	24(13.5)	56(13.2)
Residence			
Addis Ababa	177(72.2)	127(71.3)	304(71.9)
Out of Addis Ababa	68(27.8)	51(28.7)	119(28.1)
Religion			
Orthodox	186(76)	136(76)	322(76.1)
Muslim	42(17.1)	31(17.4)	73(17.3)
Catholic	1(0.4)	1(0.6)	2(0.5)
Protestant	16(6.5)	10(6)	26(6.1)

DRHs, drug related hospitalizations; non-DRHs, non-drug related hospitalizations; SD, standard deviation;

* Represent variables having significant bivariate associations.

Table 1 …. continued

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Employment status*			
Salaried worker	111(45.3)	83(46.6)	194(45.9)
Unemployed	87(35.5)	74(41.6)	161(38.1)
Student	18(7.3)	7(3.9)	25(5.9)
Other[2]	29(11.8)	14(7.9)	43(10.2)
Social habit (smoking cigarette)			
Yes	29(11.8)	15(8.4)	44(10.4)
No	216(88.2)	163(91.6)	379(89.6)
Social habit (drinking alcohol)			
Yes	71(29)	57(32)	128(30.3)
No	174(71)	121(68)	295(69.7)
Any physical activity			
Yes	170(69.4)	132(74.1)	302(71.4)
No	70(30.6)	46(25.9)	106(28.6)

[2] Others: participants who did not have any occupation rather they were lived as dependent with other people. DRH, drug related hospitalization; Non-DRH, Non-drug related hospitalization; n, number; SD, standard deviation

Table 1 …. Continued

Table 1 …. continued

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Home remedies (herbals)			
Yes	3(1.2)	0(0)	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Number of medications taken per patient *			
Mean± SD	3.4±2.4	3.2±2.1	3.3±2.3
0	24(9.8)	12(6.7)	36(8.5)
1	41(16.7)	26(14.6)	67(15.8)
2	35(14.3)	40(22.5)	75(17.7)
3-4	61(24.9)	57(32)	118(27.9)
≥5	84(34.3)	43(24.2)	127(30)
Polypharmacy			
Yes	84(34.3)	43(24.2)	127(30)
No	161(65.7)	135(75.8)	296(70)
Co morbid condition*			
Yes	137(55.9)	76(42.7)	213(50.4)
No	108(44.1)	102(57.3)	210(49.6)
Co morbid condition (Hypertension)			
Yes	68(27.8)	40(22.5)	108(25.5)
Co morbid condition (Diabetes mellitus)			
Yes	31(12.7)	22(12.4)	53(12.5)
Co morbid condition (Cardiac diseases)			
Yes	38(15.5)	21(11.8)	59(13.9)

* Represent variables having significant bivariate associations.

Prevalence and categories of drug related hospitalizations

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

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

Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Untreated indications		94(38.5)
	Untreated medical condition is existed	34(36.2)
	Synergistic/ potentiating drug needed	42(44.7)
	Preventive/ prophylactic drug needed	18(19%)
Improper Drug Selection		16(6.5)
	More effective alternative drug is available	6(37.5)
	Condition is already refractory to drug	2(12.5)
	The drug is not effective for condition	6(37.5)
	Others[4]	2(12.5)

[4] Others; patients who were using expired drugs like insulin and albuterol.

Table 2 Continued……

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Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Sub therapeutic Dosage		30(12.2)
	Wrong dose (too small) of the drug	24(80)
	Frequency is inappropriate (long)	5(16.7)
	Duration of drug use is too short	1(3.3)
Supra therapeutic Dosage		13(5.3)
	Wrong dose (too high) of the drug	11(84.6)
	Frequency is inappropriate (short)	2(15.4)
Adverse drug reaction		38(15.5)
	Undesired effect from the drug is found	34(89.5)
	Unsafe drug for patient is existed	1(2.6)
	Dosage is administered too rapidly	1(2.6)
	Allergic reactions is found/reported	2(5.3)
Drug Interactions		1(0.4)
	There is (are) major drug interaction	1(100)

[5]Others; patients who were using expired drugs like insulin and albuterol.

Table 2 Continued….

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Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Failure to receive drugs.		130(53.5)
	Does not understand instructions	6(4.6)
	Patients prefer not to take	43(33.1)
	Patients forget to take	3(2.3)
	Drug product not available	17(13.1)
	Cost of medication too expensive	16(12.3)
	Disbelieves on the drug effectiveness	1(0.8)
	Patients felt better	17(13.1)
	Patients felt worse	1(0.8)
	Fear of adverse events	18(13.8)
	Failure to follow-up due to Covid-19	8(6.2)

Total number of DRPs leading DRHs	322
Total number of participants with DRHs	245
Average number DRPs per patients with DRHs	1.31
Preventability of DRHs	215(87.8)

Medications and diseases involved in drug related hospitalizations

Out of a total of 245 drug related hospitalized patients, nearly one -third of them had cardiovascular diseases (80, 32.6%) followed by endocrine disorders (47, 19.2%) and cerebrovascular disease (26, 10.6%).

Table 3: Diseases that associated with drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

Diseasecategories	**n(%)**
Cardiovascular diseases	80 (32.6%)
CNS diseases	8 (3.2%)
Cerebrovascular disease	26(10.6%)
Infectious diseases	21 (8.5%)
Endocrine system diseases	47 (19.2%)
Diseases of cancer	25 (10.1%)
Diseases of the respiratory system	21 (8.5%)
GI diseases	10 (4%)
Others*	7 (2.8%)

*Includes anemia, chronic kidney disease, systemic lupus erythematosus and hemophilia

Medication classes and specific drugs implicated in DRHs are depicted in Table 4.

A total of 497 drugs were implicated in 245 drug-related hospitalized patients, providing an encounter of 2.03 drugs per drug-related hospitalized patient. Cardiovascular, antimicrobial, antineoplastic and endocrine drug classes were the most frequently involved drugs in the hospital admissions. Among cardiovascular drugs; furosemide (59,24.1%), angiotensin converting enzyme inhibitors (ACEIs) (48,19.1%), and antiplatelets & anticoagulants (44,18%) were the most frequently mentioned followed by drugs acting on the endocrine system like oral hypoglycemic

agents (37, 15.1%) and insulin (24, 9.8%). Antibiotics (25 ,10%), anticancer drugs (23 ,9%), and combination antiretroviral therapy (15, 6.1%) had also contributed to admission to varied extent.

Table 4: Medication classes and specific drugs implicated in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

Drugs class	Specific drugs	n (%)
Cardiovascular drugs		
	Atorvastatin	31(12.7)
	Antiplatelets(aspirin,clopidogril)	24(9.8)
	Furosemide	59(24.1)
	Spironolactone	33(13.5)
	Anticoagulants (Warfarin, heparin)	20(8.2)
	Beta blockers (metoprolol,atenolol)	21(8.6)
	Digoxin	15(6.1)
	Angiotensin converting enzyme inhibitors (enalapril/lisinopril)	48(19.6)
	Calcium channel blockers (nifedipine, amlodipine)	34(13.9)
	Hydrochlorothiazide	11(4.5)

Table 4Continued……..

Table 4 continued…..

Drugs class	Specific drugs	n (%)
Drugs act on the respiratory system		
	Long-acting beta blockers	15(6.1)
	bronchodilator	10(4.1)
Central nervous system drugs		
	Antiepileptics	5(2)

	antipsychotic	5(2)
	Amitriptylin	2(0.8)
Antimicrobial drugs		
	Antibiotics (piperacillin/tazobactam, meropenem, amoxicillin, amoxicillin /clavunicacid ,ceftriaxone, benzathine penicillin)	25(10.2)
	Combination antiretroviral therapy	15(6.1)
	Anti-tuberculosis	13(5.3)
Antineoplastic agents	Cyclophosphamide, imatinib, methotrexate, doxorubicin	23(9.4)
Immuno-suppressants		
	Mycophenolate	1(.4)
	corticosteroids (prednisolone, budesonide)	9(3.7)
Endocrine drugs		
	Oral hypoglycemic drugs (metformin, glibenclamide)	37(15.1)
	Insulin	24(9.8)
	Propylthiouracil	4(1.6)
Gastrointestinal drug	Proton pump inhibitors	7(2.9)
Others	Potassium chloride	1(0.4)
	Non-steroidal anti-inflammatory drugs	3(1.2)
	Opioid	1(0.4)

Table 4 **Continued**

Drugs class	Specific drugs	n (%)
Others		
	Ferrous sulphate	1(0.4)
Total number of medications involved in DRHs		497
Total number of participants with DRHs		245(57.9)
Average number medications per patients with DRHs		2.03

Factors associated with the occurrence of drug related hospitalizations

According to the multivariate logistic regression analysis the variables age, employment, presence of co morbid diseases and education level were significantly associated with the occurrence of DRHs (See in Table5). Age > 64 years (Adjusted Odds Ratio [AOR] = 7.451, 95%CI: 1.889-29.397), tertiary educational level (AOR=0.360, 95%CI: 0.141-0.923), participants who did not have any occupation (AOR=3.409, 95%CI: 1.120-10.374), students (AOR=6.331,95%CI:1.375-29.153) and presence of co-morbid diseases (AOR=2.004,95%CI: 1.095-3.668) were predictors of DRHs.

Table 5: **Predictors that involved in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)**

	Predictors of Patients hospitalization			**Odds Ratios**	
	[3]DRH(245)	**Non-DRH(178)**	**Total(423)**	**AOR(95% CI)**	**P-value**
Variables	**n (%)**	**n (%)**	**n (%)**		
Age (Years)					
Mean±SD	48.24±17.86		47.50±17.21		
14 - 24	24(9.8)	14(7.9)	38(8.98)	1.000	
25- 39	51(20.8)	59(33.1)	110(26)	1.55(0.51-4.66)	0.435
40 - 64	100(40.8)	74(41.6)	174(41.1)	2.567(0.82-8.06)	0.106
>64	70(28.6)	31(17.4)	101(23.9)	7.45(1.89-29.40)	**0.004**
Marital status					
Single	64(26.1)	34(19.1)	98(23.2)	1.00	
Married	129(48.6)	105(59)	234(55.3)	0.60(0.29-1.23)	0.160
Widowed	20(8.2)	9(5.1)	29(6.7)	0.49(0.20-1.18)	0.109
Divorced	42(17.1)	31(16.9)	73(17.3)	0.35(0.19-0.75)	0.983
Education level					
No formal education	116(47.3)	72(40.4)	188(44.4)	1.00	
Elementary	66(26.9)	47(26.4)	113(26.7)	0.57(0.23-1.43)	0.229
Secondary	31(12.7)	35(19.7)	66(15.6)	0.57(0.23-1.39)	0.215
Tertiary	32(13.1)	24(13.5)	56(13.2)	0.36(0.14-0.92)	**0.033**

[10]DRH, drug related hospitalization; non-DRH, non-drug related hospitalization; AOR, adjusted odds ratio; CI, confidence interval

Table 5 Continued

	Predictors of Patients hospitalization			Odds Ratios	
	DRH(245)	**Non-DRH(178)**	**Total(423)**	**AOR(95% CI)**	**P-value**
Variables	**n (%)**	**n (%)**	**n (%)**		
Employment status					
Salaried worker	111(45.3)	83(46.6)	194(45.9)	1.00	
Unemployed	87(35.5)	74(41.6)	161(38.1)	0.29(0.09-0.89)	1.000
Student	18(7.3)	7(3.9)	25(5.9)	6.33(1.38-29.15)	**0.018**
Others*	29(11.8)	14(7.9)	43(10.2)	3.41(1.12-10.37)	**0.031**
Polypharmacy					
Yes	84(34.3)	43(24.2)	127(30)	1.48(0.72-3.04)	0.284
No	161(65.7)	135(75.8)	296(70)	1.00	
Co morbid condition					
Yes	137(55.9)	76(42.7)	213(50.4)	2.00(1.09-3.67)	**0.024**
No	108(44.1)	102(57.3)	210(49.6)	1.00	

*Others: participants who did not have any occupation

DISCUSSION

The aim of optimizing pharmacotherapy is to achieve the desired therapeutic outcomes in the absence of morbidity and mortality associated with a drug. To the best of our knowledge, this study is the first to explore the prevalence, categories and rate of preventability of DRHs in the ED of three selected hospitals that are responsible for the provision of medical and surgical care to patients in need of immediate care.

The occurrence of DRHs reported in this study (245,57.9%) is substantially higher than studies conducted elsewhere, including America (16.2%), Brasil (31.6%), Denmark (10.8%), Norway(38%), Sweden (41.3%), India (17.2 %), and Malaysia (39%).[3 6 7 18-20 26 27]The high prevalence in the current study could be explained by a number of reasons: (i) The categories of DRPs causing DRHs in this study were comprehensive, whilst other studies investigated particular types of DRPs resulted DRHs such as therapeutic failure[27] and ADR [2 26 28 29]; (ii) The prospective design of this study helps to ensure the gathering all information required to accurately classify the events; (iii) Detailed histories of drug therapy obtained by clinical pharmacists might have improved detection of DRHs ; and (iv) use of the Helper's and Strand's comprehensive classification system has likely boosted the probability that all possible drug-related causes of hospitalization to be identified. In addition, the wide variability in the rate of DRHs could also be attributed to the variations in the extent of study population, inclusion criteria, study settings, participant's level of education and awareness, level of health professional expertise, methods of evaluating DRHs attributed to DRPs, study designs (prospective vs. retrospective) and the study duration. These variations are also reported by other studies.[2 10 11 28 29]

In this study, 87.8 % of DRHs were deemed to be preventable and this is in line with other international studies in which preventability of DRHs has been by far greater than fifty percent.[10-12 18 21 22 29 30] The reasons why DRHs preventability was high could be attributed to failure to taking

appropriate measurements before drug related diseases were apparent. For instance, the principal categories of DRHs in our study were failure to receive drugs (130,53.5%) and untreated indication (94, 38.5%). Hence, both DRHs attributed to DRPs could be avoided by providing awareness for patients about their drugs use, applying good prescribing and dispensing practice, and providing appropriate pharmaceutical care plan.

The majority of DRHs were most commonly seen among female patients, which is concordant with a previous study.[31] However, in a study done in Saudi Arabia, DRHs were largely found in male patients.[2 22] Elderly patients developed more DRPs leading to DRHs than patients in other age groups which is also in line with other studies.[6 16 27] The main reasons could be that increased deterioration of physiologic functions and likelihood of co-morbid conditions with age. These conditions may warrant taking of multiple drugs, which ultimately serve as basis for contracting medication side effects and interactions (drug-drug or drug-food).

In this study, patients whose education level being elementary and below were more prone to develop DRHs than having high school education or above, which was consistent with studies done previously.[3 18] This could be related to high level education is useful for better socioeconomic status and to understand about appropriate medications use

Out of a total of 245 patients with DRHs, the foremost categories of DRHs were failure to receive drugs (130,53.5%) followed by untreated indication (94,38.5%), adverse drug reactions (38,15.5%) and sub therapeutic dosage (30,12.2%). Similar findings were reported by other studies.[5 12 18 20-22 25 27 30] The major reasons for failure to receive drugs in this study were preference to cultural and religious therapies over conventional medicines, drug products were not available, cost of medications was too expensive, fear of adverse events, failure to follow-up due to Covid-19, felt better and illiteracy (near to half of patients with DRHs were illiterate). Thus, inability to

recall regimens is another important reason associated with increased risk of hospitalization related to failure to receive drugs, as reported elsewhere.[3 11 21]

The second frequent category of DRHs was untreated indication (94, 38.5%) as reported in other studies.[9 22] Reasons were patients remained untreated; prophylaxis and synergistic medications were not indicated. This might be due to incorrect diagnosis; patients didn't come to health setting timely and treating physicians did not follow the management guidelines/protocols. For example, patients having moderate persistent asthma were being treated with albuterol inhalation alone. Statins have not also been prescribed for patients with atherosclerotic cardiovascular disease (ASCVDs) like peripheral arterial disease, stroke, ischemic heart disease and whose age ≥ 40 years with diabetes mellitus and high low density lipoprotein level as per the guidelines. In addition, some compelling indication like hypertension remains untreated and subsequently results in DRHs owing to stroke and others cardiovascular diseases. Furthermore, since only cancer diagnosis and management are carried out in one of this research setting hospital, which is TASH, patients coming from different corners of the country remained untreated and/or treated with various empirical therapies that also lead to improper drug selection until they start anti-cancer drugs in TASH.

ADRs (38, 15.5%) were also commonly reported as the common classifications of DRHs, which is also mentioned with other studies.[11 19-21 29 30 32] This might be associated with numerous number of cardiac and diabetic patients in our study population and poor awareness of patients with regard to cardiac medications untoward effects such as diuretics induced electrolytes disturbance and hypoglycemic symptoms of antidiabetics. Some ADRs could be resulted from failure to follow direction for use of the medications. For example, diabetes mellitus patient who was on metformin experienced epigastric burning sensation pain and vomiting after taking metformin without meal. Overall, the plausible explanations for DRHs might be the absence of pharmaceutical care services

in many health institutions including emergency wards of the study settings, which is very important for optimizing drug therapy and patient safety. There was also poor collaboration among patients, clinical pharmacists and physicians about patient's medications use process involving medications use, their side effects, adherence issue and consequences of not taking their medication properly. Therefore, the better opportunity for clinical pharmacists to add value in patient care roles is through ensuring medication management services according to evidence-based guidelines. In the present study, both failure to receive drugs and untreated indication were reported under the DRPs category of need additional drug therapy that resulted in DRHs, which is supported by other studies.[7 9 18]

In this study, medication classes frequently observed to cause DRHs were cardiovascular medicines, antimicrobial, antineoplastic, endocrine drugs, respiratory medicines and central nervous system drugs. Among these classes of drugs, cardiovascular drug were predominantly involved in DRHs which was in line with other studies.[3 5 6 21 25 27]Cardiovascular drugs, antidiabetics, and antiasthmatics were most commonly associated with DRHs was supported in the previous studies.[2 24 26 27] The most common drugs associated with DRHs mentioned in this study finding were furousemide, ACEIs ,insulins, oral hypoglycemic agents, warfarin, spironolactone ,aspirin and central nervous system agent and these are also implicated in several other studies.[5 7 10 21 22 24 29]The main reason might be connected with the common diseases of the study area which were heart failure, diabetes mellitus, stroke, human immunodeficiency virus and asthma.

Moreover, the most common organ system involved in DRHs was the cardiovascular system (80, 32.6%), with the most common specific disease of heart failure (55, 22.5%) which is consistent with previous studies.[6 25] Moreover, hypertension was mentioned for DRHs which was implicated in the previous study.[5 22 27]This is due to the fact that cardiovascular diseases require multiple

medicine regimens and this contributed to DRPs. Among hospitalized patients attributed to endocrine systems were due to hypoglycemia, hyperglycemia and diabetic ketoacidosis, which are also cited in other studies.[22 27]It might be due to the patients poor awareness about the hypoglycemic symptoms of anti-hypoglycemic agents , poor monitoring control and patients prefer not to take the medications.

In this study, age, educational level and presence of comorbid diseases had statistically significant correlation with the occurrence of DRHs. The findings are consistent with other studies.[18 20 30 33]

In multiple binary logistic regression analysis, patients with ≥ 65 years of age were 7.45 times more likely to be hospitalized due to drug related morbidity than non-drug related as compared to age between 14 and 24 years. This might be owing to age-related physiological changes, larger number of coexisting disease conditions, which require multiple medications and this in turn is associated with an increased risk of DRHs.

From employment factor, students were 6.3 folds high likely exposed to DRHs than non-drug related as compared to the employed. This might be explained by the nature of the disease they had which means students in this finding have majorly contracted heart failure disease secondary to chronic rheumatoid valvular heart disease. Out of a total 16 students, 9 (56.3%) of them had heart failure owing to valvular heart diseases. Consequently, it needs lifelong and multiple medications treatment and then they faced various DRPs leading hospitalizations. Moreover, participants who did not have any occupation were 3.4 times high likely to be hospitalized owing to drug related diseases than non-drug related as compared to employed.

The other factor was education level in which patients with tertiary education level were 64% less likely to be hospitalized with drug related hospitalizations as compared to participants who did not have formal education. This could be related to high level education might be useful to understand

about appropriate medications use. This was supported by the studies conducted at Brasil.[3 11 18] Patients with co-morbid disease were also 2 folds high likely to be drug related hospitalized than non-drug related as compared to patients without co morbid disease. As implicated in the previous studies,[18 30 33] co- morbidity increases the vulnerability towards DRPs. These results clearly indicate the necessity of managing DRHs in multimorbid patients.

In terms of drug related hospital stay, the overall length of the hospital stay in the present study was 4352 days with the average length of hospital stay 10.28±8.99 days, which is longer than what has been reported in other study.[12] This was might be owing to the data in the previous study is in a single hospital and for a relatively short period of time (28 days) while in this finding, the study was carried out at three tertiary care hospitals for the periods of 60 days. Therefore, avoiding preventable DRHs is also a very cost-effective tool for health care systems and could reduce the problem of bed crisis in hospitals.

Among factors which have not demonstrated an association in multivariate analysis, polypharmacy was mentioned. This agree with what have been reported in other studies.[21 25] In contrast, polypharmacy has been reported having positive association with the occurrence of DRHs in previous studies.[3 6 11 21 22 30] This lack of significance could be resulted from variations in number of used medications and identified DRPs for causing DRHs. In this study, around two third of the patients with DRHs used from none to four drugs per patient. Accordingly, to say polypharmacy; ≥ five drugs should be concomitantly taken. Furthermore, the identified DRPs causing DRHs were failure to receive drugs and untreated indication. So, both categories reveal not taking medications and the patients might not use polypharmacy. Additionally; marital status did not illustrate significant association with DRHs.

Conclusion

The prevalence of DRHs was higher than studies conducted elsewhere among emergency ward patients in the study settings. Among those, majority of DRHs were deemed to be preventable. These findings provide valuable insight about category of DRPs and class of drugs that causes DRHs. Age, educational level, participants who did not have any occupation and presence of co-morbid condition have had significant association with DRHs. Hence, researches regarding DRHs should be conducted in different Ethiopian hospitals to demonstrate its impact.

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Contributors

ABB and MBD contributed to conceptualization, design, analysis and write up. MBD organized the collection of data for analysis and write up the draft manuscript. ABB and MBD supervised the collection data and overall research work including interpretation of results, reviewed and revised critically the manuscript. Both authors approved the final version to be submitted for publication.

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Competing interests

There are no conflicts of interest.

Patient consent for publication Not required

Ethics approval

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

Data availability statement

Data are accessed upon reasonable request of the corresponding author. All relevant data are within the manuscript and Supporting Information files.

Provenance and peer review

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

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

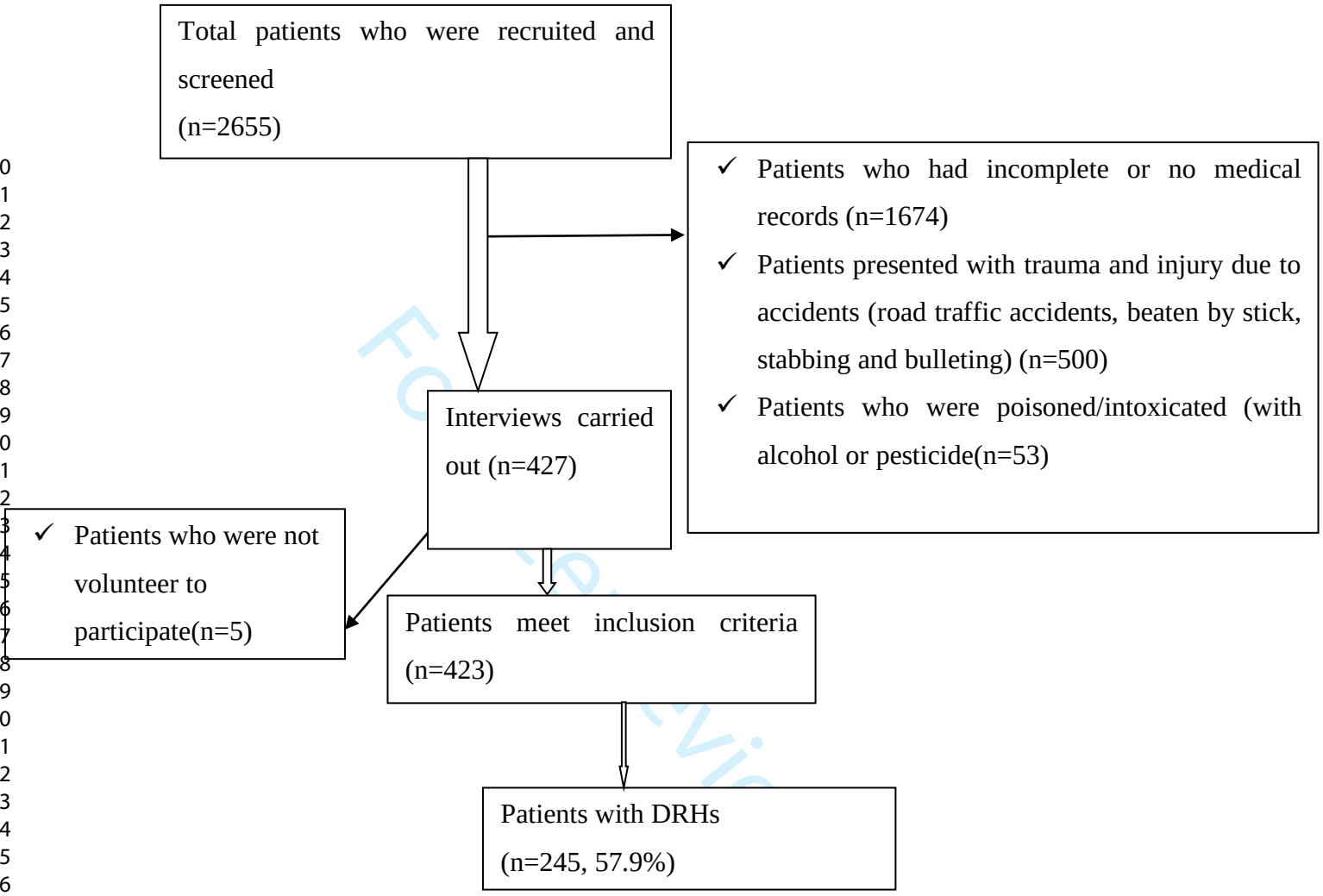

Figure 1

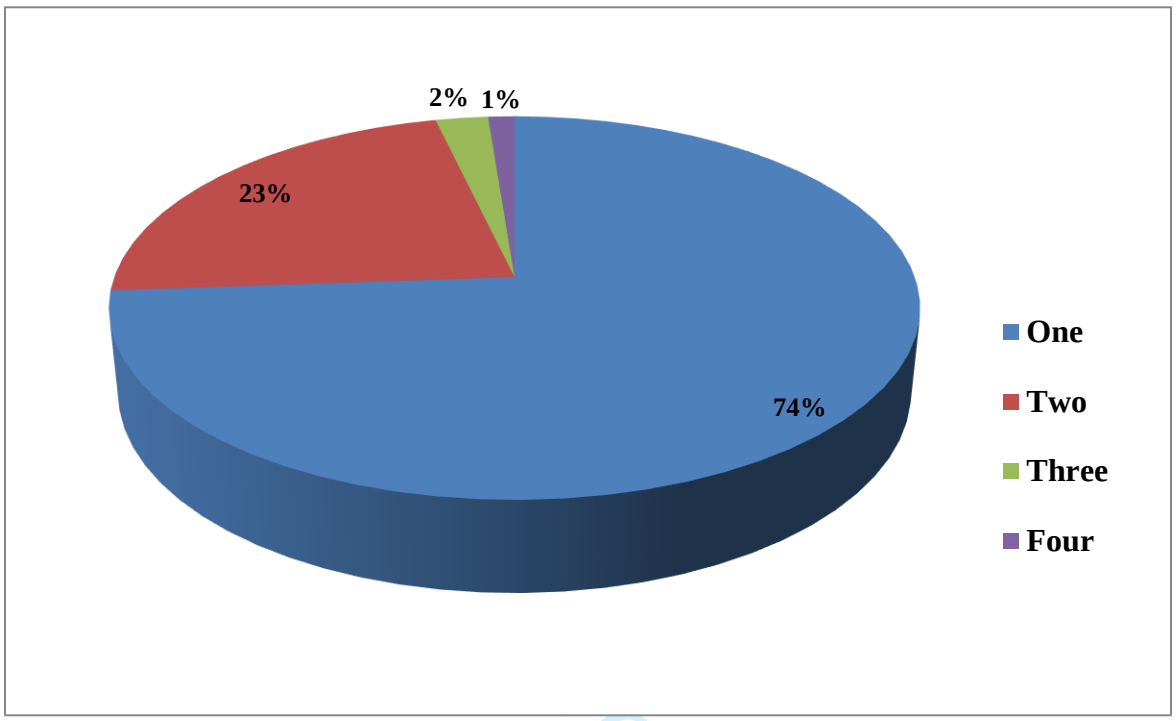

Figure 2

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Prevalence and Predictors of Drug-Related Hospitalizations among Patients Visiting Emergency Departments of Addis Ababa City Hospitals in Ethiopia: A Multicenter Prospective Observational Study

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ABSTRACT

Objectives: This study aimed to determine the prevalence, categories, and predictors of drug-related hospitalizations (DRHs) among patients visiting emergency departments of Addis Ababa city hospitals, Ethiopia.

Design: A multicenter prospective observational study was conducted through patients interview and chart review.

Settings: The study was undertaken in three tertiary care hospitals, Addis Ababa, Ethiopia.

Participants: A total of 423 patients fulfilling the inclusion criteria were included.

Outcome measures: Prevalence and preventability of DRHs, categories of drug-related problems causing DRHs, medications, and diseases involved in DRHs, and factors significantly associated with DRHs.

Result: More than half of the patients (216, 51.1%) were females. The mean age (SD) was 47.50 (±17.21) years. The mean length of hospital stay (SD) was 10.29(±8.99) days. Nearly, 60% (249) of them were hospitalized due to drug-related problems, of which 87.8% were preventable. The cause for hospitalization for more than half (130, 53%) of them was a failure to receive drugs, and 37.85 (94) patients were categorized as untreated indications. Age ≥ 65 years (Adjusted Odds Ratio [AOR]=7.451,95%CI: 1.889-29.397), tertiary educational level (AOR=0.360, 95%CI: 0.141-

0.923), participants who did not have any occupation (AOR=3.409, 95%CI: 1.120-10.374) and presence of co-morbid conditions (AOR=2.004, 95%CI: 1.095-3.668) were predictors of DRHs.

Conclusion: Nearly 90% of DRHs were deemed to be preventable in the study settings. Older age, lower educational level, unemployment, and presence of the co-morbid condition in hospital as an inpatient were predictors of DRHs**.**

Strength and limitations of the study

- The strength of this study is the study design which is a prospective observational study.
- This is a multicenter study with sufficient sample size, increasing representativeness the findings.
- The main limitation of this study is lack of standardized procedures for immediate recording and reporting of DRHs.
- Patients who visited other than the emergency ward were excluded from participation can also be considered as a limitation of the study.

INTRODUCTION

Though drugs can be ordered for the intention of achieving desired health outcomes that improve patients quality of life, symptoms and signs of diseases causing drug related hospitalizations (DRHs) as a result of drug related problems (DRPs) could be apparent.[1-3] DRP is defined according to Helper and strand as 'an undesired event or circumstance due to drug therapy that actually or potentially interferes with desired health outcomes'.[4]

Medication's use has been increasing across the globe due to the presence of large number of treatable diseases and this has contributed to production of more advanced medications by the pharmaceutical industries. Therefore, advances in drug therapies could lead to an apparent increase in the incidence of DRPs, which in turn lead to hospitalization[5]. Hospitalization can be defined as drug related if it is straightforwardly linked to one of the eight predefined Helper's and Strand's classifications of DRPs: adverse drug reaction (ADR), drug interaction, improper drug selection, untreated indication, sub-therapeutic dosage, supra-therapeutic dosage, failure to receive drugs, and drug use without indication.[6-12] Those DRPs can arise when a medicine is prescribed aptly and used correctly (e.g., ADR), due to errors involving prescribing (including inappropriate or over-treatment, and failure to prescribe the indicated treatment or under-treatment), dispensing, administering, reconciling, or monitoring of medicines as well as from poor patient adherence.[2 13 14] According to the World Health Organization (WHO), an ADR is any harmful, undesired and inadvertent drug effect that occurs at doses used in human for therapy, diagnosis or prophylaxis.[15]

Over the past decades, DRHs have been considered as wide spreading[16]. In the United States, DRPs accounted for 17 million emergency department (ED) visits and 8.7 hospitalizations annually.[17] It increases morbidity and mortality rates, health care cost, decreases income and household productivity and reduced quality of life.[2 18 19]

Studies carried out in different areas of the globe estimated the extent of DRHs to be between 16% to 41.3%. Of these, 50% to 95% were preventable. Supratherapeutic dosage (10.3%-12.7%), non-compliance (10.6%-65.8%), ADRs (10.7%-45.5%) and untreated indications (10.7-13.3%) were frequently identified as the causes of DRHs.[6 9 18 20-22]

DRPs resulting DRHs were defined as preventable if the patient failed to take a drug that is known to reduce or prevent symptoms according to the prescribed directions, took a drug for which a patient had a known allergy, drug treatment was obviously improper, dosage differed from accepted recommendations, took a drug that was not indicated, and if there was a failure to monitor by a physician at reasonable time intervals due to financial difficulty. If there was, however, no reasonable actions to prevent DRPs, it is then termed as non-preventable.[20 23]

In many studies, patients with DRHs had mainly cardiovascular diseases and diabetes, suggesting that cardiovascular and hypoglycemic medications were involved in DRHs.[6 10 11 18 20 21 24 25] Previous studies also identified polypharmacy, advanced age and comorbid conditions as factors that favor the occurrence of DRHs.[3 6 20 21]

It is thus important to determine DRHs prevalence to improve treatment outcomes and prevent unnecessary admissions. To the best of our knowledge, there are no studies conducted about DRHs in Ethiopia. The present study therefore aimed to determine the prevalence, categories and predictors of DRHs among patients admitted to an ED of three selected hospitals in Addis Ababa, the capital of Ethiopia.

METHODS

Study Settings

The study was carried out in the ED of Tikur Anbessa Specialized Hospital (TASH), Zewditu Memorial Hospital (ZMH), and Yekatit 12 Hospital Medical College (Y12HMC), Addis Ababa, Ethiopia. TASH has 700 beds and it is a tertiary care teaching hospital affiliated with Addis Ababa University. In TASH, outpatient, inpatient, and emergency services are delivered. The ED provides services for about 13,920 patients per year. Y12HMC is also a tertiary carry level referral and teaching hospital that provides both inpatient and outpatient treatment for a large number of people coming from Addis Ababa as well as other places of the country. The hospital has a total of three ED rooms. The adult medical ED is collocated with adult surgical ED. It serves around 10,560 patients per year. The third hospital is ZMH, which is one of the teaching and general referral hospitals in Ethiopia and the ED serves about 10,560 patients per year.

Patient involvement

Patients did not participate in the initial conception and design of the study. However, based on the participating patients' comments during the pretest (5% of the sample size), we made a correction on the patient approach and timing for an interview at ED during data collection. Patients who participated actively in this study determined the medication use, level of adherence, and medical history.

Study design and population

A prospective observational study design was used to collect data from August to September, 2020. All patients admitted to the ED of the three selected hospitals during the study period and fulfilled the inclusion criteria were included.

Inclusion and exclusion criteria

Patients having a medical history with completed data and ≥ 14 years old were included. Patients with incomplete or no medical records, refused to participate, presented with trauma and injuries associated with accidents (e.g. road traffic accidents, beaten by stick, stabbing and bulleting) and poisoned/intoxicated (for instance snake bite, alcohol intoxication or use of pesticide) were excluded. During data collection periods, about 2655 patients were being admitted to the ED, out of which 423 participants fulfilled the inclusion criteria

Sample size determination and techniques

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

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

(Hence; n = required sample size, Zα/2 = critical value for normal distribution at 95% confidence interval, which equals 1.96 (*Z* value at alpha = 0.05), P = Proportion of DRH =0.5, d = margin of error of 5%=0.05. The calculated sample size using this formula was 384. Adding 10% contingency (for non-response rate) to compensate participants who could refuse to participate, brought the final sample size to 423. The sample size was distributed to the three hospitals based on the patient load of hospital's ED per annum as mentioned in the Study settings. Accordingly, 169 participants were included from TASH, 127 participants from ZMH and 127 participants from Y12MHC.

Data collection procedures

A structured questionnaire was developed from carefully evaluated published articles in the literature. For instance, categories of DRPs that leads to hospitalization and factors having association with DRH (e.g. socio-demographic and clinical characteristics) were extracted from

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

Data were collected by three pharmacists having Master of Science degrees in Clinical Pharmacy. They had basic knowledge and skill in pharmaceutical care services and also received training on how to obtain data from patients' medication charts and approach the patients and health care professionals. Updated Ethiopian Standard Treatment Guidelines for Hospitals, third edition, 2014, Ethiopian Antiretroviral Therapy and Tuberculosis Guidelines, Cancer Treatment Protocols prepared by TASH Oncologists, Pharmacotherapy textbooks, Medscape, UpToDate were used as a guide for diseases management. Micromedex online database was used to check drug interactions. Furthermore, updated guidelines released from American Cardiology Center, American Heart Association, European Cardiology Society, American Diabetic Association were used as a guide to treat different diseases. Clinical pharmacists along with physicians determined subtherapeutic and supratherapeutic dosage outcomes using medical charts, laboratory tests, clinical outcomes, medication dose and frequency. Participant's hospitalization attributed to failure to receive drugs was decided using physician's recording documentation, clinical pharmacists' knowledge and patients reporting evidence. Untreated indications and improper drug

selection were evaluated and interpreted using treatment guidelines. For instance, if patients presented with untreated or improperly treated cardiac diseases, treatment was initiated and optimized using the American Heart Association guidelines, and UpToDate latest version. To minimize bias, the three pharmacists at each hospital independently evaluated the identified DRPs resulted hospitalizations. Decision was then reached by reaching consensus after a series of meetings and discussions as well consultations with physicians and residents. Once DRPs resulting DRHs were identified, they were recorded and classified using DRPs registration format according to Helper's and Strand's classification.

Data collection management

Pretest was performed on 5% patients in TASH prior to the actual data collection period and amendment was made accordingly. The data collection process was supervised, and the information gathered via data abstraction formats were reviewed and cheeked for their completeness every day to ensure quality. Urgent correction was made, if any errors were identified.

Data analysis

The data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 26. Mean and standard deviation for continuous variables and frequency and percentage for categorical variables were computed by using descriptive statistics in SPSS to summarize socio-demographic and relevant clinical characteristics of the study participants. Tables and charts were used to present the results. Furthermore, univariate and multiple binary logistic regressions were performed to analyze factors that predict DRHs. Variables with p-values < 0.2 in the binary univariate analysis were included in the multiple binary logistic regressions to control the effect of confounders. The level of significance was set at p–value ≤ 0.05 and results were reported as odds ratios (OR) with 95% confidence intervals.

RESULTS

Socio-demographic and clinical characteristics

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

Socio-demographic and clinical characteristics of the participants is depicted in Table 1. More than half of the participants (216, 51.1%) were females. The mean (SD) age of the participants was 47.5 (±17.21) years and nearly two third (275, 65%) were ≥ 40 years of age. More than 70 % (301, 71.1%) of the total participants' level of education was below secondary school. Nearly three-quarter of them (304, 71.9%) resided in Addis Ababa city. Out of the total study participants, 58% (245) of them were taking ≥3 and 30% (127) ≥ five drugs prior to admission, which is termed as polypharmacy. Above half of the participants (213, 50.4%) had co-morbid diseases, including hypertension (108, 22.5%), cardiac diseases (59, 13.5%) and diabetes mellitus (53, 12.5%). The mean (SD) length of hospital stay was 10.28±8.99 days and ranges from 2 to 96 days.

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

Variables	[1]DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Gender			
Male	119(48.6)	88(49.4)	207(48.9)
Female	126(51.4)	90(50.6)	216(51.1)
Age* (in years)			
Mean± SD	48.23±17.85	46.5±16.3	47.5±17.2
14 - 24	24(9.8)	14(7.9)	38(8.98)
25- 39	51(20.8)	59(33.1)	110(26)
40 - 64	100(40.8)	74(41.6)	174(41.1)
>64	70(28.6)	31(17.4)	101(23.9)
Marital status*			
Single	64(26.1)	34(19.1)	98(23.2)
Married	129(48.6)	105(59)	234(55.3)
widowed	20(8.2)	9(5.1)	29(6.7)
Divorced	42(17.1)	31(16.9)	73(17.3)
Education level*			
No formal education	116(47.3)	72(40.4)	188(44.4)
Elementary	66(26.9)	47(26.4)	113(26.7)
Secondary	31(12.7)	35(19.7)	66(15.6)
Tertiary	32(13.1)	24(13.5)	56(13.2)
Residence			
Addis Ababa	177(72.2)	127(71.3)	304(71.9)
Out of Addis Ababa	68(27.8)	51(28.7)	119(28.1)
Religion			
Orthodox	186(76)	136(76)	322(76.1)
Muslim	42(17.1)	31(17.4)	73(17.3)
Catholic	1(0.4)	1(0.6)	2(0.5)
Protestant	16(6.5)	10(6)	26(6.1)

DRHs, drug related hospitalizations; non-DRHs, non-drug related hospitalizations; SD, standard deviation;

* Represent variables having significant bivariate associations.

Table 1 …. continued

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Employment status*			
Salaried worker	111(45.3)	83(46.6)	194(45.9)
Unemployed	87(35.5)	74(41.6)	161(38.1)
Student	18(7.3)	7(3.9)	25(5.9)
Other[2]	29(11.8)	14(7.9)	43(10.2)
Social habit (smoking cigarette)			
Yes	29(11.8)	15(8.4)	44(10.4)
No	216(88.2)	163(91.6)	379(89.6)
Social habit (drinking alcohol)			
Yes	71(29)	57(32)	128(30.3)
No	174(71)	121(68)	295(69.7)
Any physical activity			
Yes	170(69.4)	132(74.1)	302(71.4)
No	70(30.6)	46(25.9)	106(28.6)

[2] Others: participants who did not have any occupation rather they were lived as dependent with other people. DRH, drug related hospitalization; Non-DRH, Non-drug related hospitalization; n, number; SD, standard deviation

Table 1 …. Continued

Table 1 …. continued

Variables	DRHs (245), n (%)	Non-DRHs (178), n (%)	Total (423), n (%)
Home remedies (herbals)			
Yes	3(1.2)	0(0)	3(0.7)
No	242(98.8)	178(100)	420(99.3)
Number of medications taken per patient *			
Mean± SD	3.4±2.4	3.2±2.1	3.3±2.3
0	24(9.8)	12(6.7)	36(8.5)
1	41(16.7)	26(14.6)	67(15.8)
2	35(14.3)	40(22.5)	75(17.7)
3-4	61(24.9)	57(32)	118(27.9)
≥5	84(34.3)	43(24.2)	127(30)
Polypharmacy			
Yes	84(34.3)	43(24.2)	127(30)
No	161(65.7)	135(75.8)	296(70)
Co morbid condition*			
Yes	137(55.9)	76(42.7)	213(50.4)
No	108(44.1)	102(57.3)	210(49.6)
Co morbid condition (Hypertension)			
Yes	68(27.8)	40(22.5)	108(25.5)
Co morbid condition (Diabetes mellitus)			
Yes	31(12.7)	22(12.4)	53(12.5)
Co morbid condition (Cardiac diseases)			
Yes	38(15.5)	21(11.8)	59(13.9)

* Represent variables having significant bivariate associations.

Prevalence and categories of drug related hospitalizations

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

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

Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Untreated indications		94(38.5)
	Untreated medical condition is existed	34(36.2)
	Synergistic/ potentiating drug needed	42(44.7)
	Preventive/ prophylactic drug needed	18(19%)
Improper Drug Selection		16(6.5)
	More effective alternative drug is available	6(37.5)
	Condition is already refractory to drug	2(12.5)
	The drug is not effective for condition	6(37.5)
	Others[4]	2(12.5)

[4] Others; patients who were using expired drugs like insulin and albuterol.

Table 2 Continued……

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Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Sub therapeutic Dosage		30(12.2)
	Wrong dose (too small) of the drug	24(80)
	Frequency is inappropriate (long)	5(16.7)
	Duration of drug use is too short	1(3.3)
Supra therapeutic Dosage		13(5.3)
	Wrong dose (too high) of the drug	11(84.6)
	Frequency is inappropriate (short)	2(15.4)
Adverse drug reaction		38(15.5)
	Undesired effect from the drug is found	34(89.5)
	Unsafe drug for patient is existed	1(2.6)
	Dosage is administered too rapidly	1(2.6)
	Allergic reactions is found/reported	2(5.3)
Drug Interactions		1(0.4)
	There is (are) major drug interaction	1(100)

[5]Others; patients who were using expired drugs like insulin and albuterol.

Table 2 Continued….

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Categories of DRHs	Causes of drug related hospitalizations	Frequency (%)
Failure to receive drugs.		130(53.5)
	Does not understand instructions	6(4.6)
	Patients prefer not to take	43(33.1)
	Patients forget to take	3(2.3)
	Drug product not available	17(13.1)
	Cost of medication too expensive	16(12.3)
	Disbelieves on the drug effectiveness	1(0.8)
	Patients felt better	17(13.1)
	Patients felt worse	1(0.8)
	Fear of adverse events	18(13.8)
	Failure to follow-up due to Covid-19	8(6.2)

Total number of DRPs leading DRHs	322
Total number of participants with DRHs	245
Average number DRPs per patients with DRHs	1.31
Preventability of DRHs	215(87.8)

Medications and diseases involved in drug related hospitalizations

Out of a total of 245 drug related hospitalized patients, nearly one -third of them had cardiovascular diseases (80, 32.6%) followed by endocrine disorders (47, 19.2%) and cerebrovascular disease (26, 10.6%). (See in Table 3)

Table 3: Diseases that associated with drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

Diseasecategories	**n(%)**
Cardiovascular diseases	80 (32.6%)
CNS diseases	8 (3.2%)
Cerebrovascular disease	26(10.6%)
Infectious diseases	21 (8.5%)
Endocrine system diseases	47 (19.2%)
Diseases of cancer	25 (10.1%)
Diseases of the respiratory system	21 (8.5%)
GI diseases	10 (4%)
Others*	7 (2.8%)

*Includes anemia, chronic kidney disease, systemic lupus erythematosus and hemophilia

Medication classes and specific drugs implicated in DRHs are depicted in Table 4.

A total of 497 drugs were implicated in 245 drug-related hospitalized patients, providing an encounter of 2.03 drugs per drug-related hospitalized patient. Cardiovascular, antimicrobial, antineoplastic and endocrine drug classes were the most frequently involved drugs in the hospital admissions. Among cardiovascular drugs; furosemide (59,24.1%), angiotensin converting enzyme inhibitors (ACEIs) (48,19.1%), and antiplatelets & anticoagulants (44,18%) were the most frequently mentioned followed by drugs acting on the endocrine system like oral hypoglycemic

agents (37, 15.1%) and insulin (24, 9.8%). Antibiotics (25 ,10%), anticancer drugs (23 ,9%), and combination antiretroviral therapy (15, 6.1%) had also contributed to admission to varied extent.

Table 4: Medication classes and specific drugs implicated in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)

Drugs class	Specific drugs	n (%)
Cardiovascular drugs		
	Atorvastatin	31(12.7)
	Antiplatelets(aspirin,clopidogril)	24(9.8)
	Furosemide	59(24.1)
	Spironolactone	33(13.5)
	Anticoagulants (Warfarin, heparin)	20(8.2)
	Beta blockers (metoprolol,atenolol)	21(8.6)
	Digoxin	15(6.1)
	Angiotensin converting enzyme inhibitors (enalapril/lisinopril)	48(19.6)
	Calcium channel blockers (nifedipine, amlodipine)	34(13.9)
	Hydrochlorothiazide	11(4.5)

Table 4Continued……..

Table 4 continued…..

Drugs class	Specific drugs	n (%)
Drugs act on the respiratory system		
	Long-acting beta blockers	15(6.1)
	bronchodilator	10(4.1)
Central nervous system drugs		
	Antiepileptics	5(2)
	antipsychotic	5(2)

	Amitriptylin	2(0.8)
Antimicrobial drugs		
	Antibiotics (piperacillin/tazobactam, meropenem, amoxicillin, amoxicillin /clavunicacid, ceftriaxone, benzathine penicillin)	25(10.2)
	Combination antiretroviral therapy	15(6.1)
	Anti-tuberculosis	13(5.3)
Antineoplastic agents	Cyclophosphamide, imatinib, methotrexate, doxorubicin	23(9.4)
Immuno-suppressants		
	Mycophenolate	1(.4)
	corticosteroids (prednisolone, budesonide)	9(3.7)
Endocrine drugs		
	Oral hypoglycemic drugs (metformin, glibenclamide)	37(15.1)
	Insulin	24(9.8)
	Propylthiouracil	4(1.6)
Gastrointestinal drug	Proton pump inhibitors	7(2.9)
Others	Potassium chloride	1(0.4)
	Non-steroidal anti-inflammatory drugs	3(1.2)
	Opioid	1(0.4)

Table 4 **Continued**

Drugs class	Specific drugs	n (%)
Others		
	Ferrous sulphate	1(0.4)
Total number of medications involved in DRHs		497
Total number of participants with DRHs		245(57.9)
Average number medications per patients with DRHs		2.03

Factors associated with the occurrence of drug related hospitalizations

According to the multivariate logistic regression analysis the variables age, employment, presence of co morbid diseases and education level were significantly associated with the occurrence of DRHs (See in Table5). Age > 64 years (Adjusted Odds Ratio [AOR] = 7.451, 95%CI: 1.889-29.397), tertiary educational level (AOR=0.360, 95%CI: 0.141-0.923), participants who did not have any occupation (AOR=3.409, 95%CI: 1.120-10.374), students (AOR=6.331,95%CI:1.375-29.153) and presence of co-morbid diseases (AOR=2.004,95%CI: 1.095-3.668) were predictors of DRHs.

Table 5: **Predictors that involved in drug related hospitalizations in emergency ward at TASH, ZMH and Y12HMC, Addis Ababa, Ethiopia, August to September, 2020 (n= 245)**

	Predictors of Patients hospitalization			**Odds Ratios**	
	[3]DRH(245)	**Non-DRH(178)**	**Total(423)**	**AOR(95% CI)**	**P-value**
Variables	**n (%)**	**n (%)**	**n (%)**		
Age (Years)					
Mean±SD	48.24±17.86		47.50±17.21		
14 - 24	24(9.8)	14(7.9)	38(8.98)	1.000	
25- 39	51(20.8)	59(33.1)	110(26)	1.55(0.51-4.66)	0.435
40 - 64	100(40.8)	74(41.6)	174(41.1)	2.567(0.82-8.06)	0.106
>64	70(28.6)	31(17.4)	101(23.9)	7.45(1.89-29.40)	**0.004**
Marital status					
Single	64(26.1)	34(19.1)	98(23.2)	1.00	
Married	129(48.6)	105(59)	234(55.3)	0.60(0.29-1.23)	0.160
Widowed	20(8.2)	9(5.1)	29(6.7)	0.49(0.20-1.18)	0.109
Divorced	42(17.1)	31(16.9)	73(17.3)	0.35(0.19-0.75)	0.983
Education level					
No formal education	116(47.3)	72(40.4)	188(44.4)	1.00	
Elementary	66(26.9)	47(26.4)	113(26.7)	0.57(0.23-1.43)	0.229
Secondary	31(12.7)	35(19.7)	66(15.6)	0.57(0.23-1.39)	0.215
Tertiary	32(13.1)	24(13.5)	56(13.2)	0.36(0.14-0.92)	**0.033**

[10]DRH, drug related hospitalization; non-DRH, non-drug related hospitalization; AOR, adjusted odds ratio; CI, confidence interval

Table 5 Continued

	Predictors of Patients hospitalization			Odds Ratios	
	DRH(245)	**Non-DRH(178)**	**Total(423)**	**AOR(95% CI)**	**P-value**
Variables	**n (%)**	**n (%)**	**n (%)**		
Employment status					
Salaried worker	111(45.3)	83(46.6)	194(45.9)	1.00	
Unemployed	87(35.5)	74(41.6)	161(38.1)	0.29(0.09-0.89)	1.000
Student	18(7.3)	7(3.9)	25(5.9)	6.33(1.38-29.15)	**0.018**
Others*	29(11.8)	14(7.9)	43(10.2)	3.41(1.12-10.37)	**0.031**
Polypharmacy					
Yes	84(34.3)	43(24.2)	127(30)	1.48(0.72-3.04)	0.284
No	161(65.7)	135(75.8)	296(70)	1.00	
Co morbid condition					
Yes	137(55.9)	76(42.7)	213(50.4)	2.00(1.09-3.67)	**0.024**
No	108(44.1)	102(57.3)	210(49.6)	1.00	

*Others: participants who did not have any occupation

DISCUSSION

The aim of optimizing pharmacotherapy is to achieve the desired therapeutic outcomes in the absence of morbidity and mortality associated with a drug. To the best of our knowledge, this study is the first to explore the prevalence, categories and rate of preventability of DRHs in the ED of three selected hospitals that are responsible for the provision of medical and surgical care to patients in need of immediate care.

The occurrence of DRHs reported in this study (245,57.9%) is substantially higher than studies conducted elsewhere, including America (16.2%), Brasil (31.6%), Denmark (10.8%), Norway(38%), Sweden (41.3%), India (17.2 %), and Malaysia (39%).[3 6 7 18-20 26 27]The high prevalence in the current study could be explained by a number of reasons: (i) The categories of DRPs causing DRHs in this study were comprehensive, whilst other studies investigated particular types of DRPs resulted DRHs such as therapeutic failure[27] and ADR [2 26 28 29]; (ii) The prospective design of this study helps to ensure the gathering all information required to accurately classify the events; (iii) Detailed histories of drug therapy obtained by clinical pharmacists might have improved detection of DRHs ; and (iv) use of the Helper's and Strand's comprehensive classification system has likely boosted the probability that all possible drug-related causes of hospitalization to be identified. In addition, the wide variability in the rate of DRHs could also be attributed to the variations in the extent of study population, inclusion criteria, study settings, participant's level of education and awareness, level of health professional expertise, methods of evaluating DRHs attributed to DRPs, study designs (prospective vs. retrospective) and the study duration. These variations are also reported by other studies.[2 10 11 28 29]

In this study, 87.8 % of DRHs were deemed to be preventable and this is in line with other international studies in which preventability of DRHs has been by far greater than fifty percent.[10-12 18 21 22 29 30] The reasons why DRHs preventability was high could be attributed to failure to taking

appropriate measurements before drug related diseases were apparent. For instance, the principal categories of DRHs in our study were failure to receive drugs (130,53.5%) and untreated indication (94, 38.5%). Hence, both DRHs attributed to DRPs could be avoided by providing awareness for patients about their drugs use, applying good prescribing and dispensing practice, and providing appropriate pharmaceutical care plan.

The majority of DRHs were most commonly seen among female patients, which is concordant with a previous study.[31] However, in a study done in Saudi Arabia, DRHs were largely found in male patients.[2 22] Elderly patients developed more DRPs leading to DRHs than patients in other age groups which is also in line with other studies.[6 16 27] The main reasons could be that increased deterioration of physiologic functions and likelihood of co-morbid conditions with age. These conditions may warrant taking of multiple drugs, which ultimately serve as basis for contracting medication side effects and interactions (drug-drug or drug-food).

In this study, patients whose education level being elementary and below were more prone to develop DRHs than having high school education or above, which was consistent with studies done previously.[3 18] This could be related to high level education is useful for better socioeconomic status and to understand about appropriate medications use

Out of a total of 245 patients with DRHs, the foremost categories of DRHs were failure to receive drugs (130,53.5%) followed by untreated indication (94,38.5%), adverse drug reactions (38,15.5%) and sub therapeutic dosage (30,12.2%). Similar findings were reported by other studies.[5 12 18 20-22 25 27 30] The major reasons for failure to receive drugs in this study were preference to cultural and religious therapies over conventional medicines, drug products were not available, cost of medications was too expensive, fear of adverse events, failure to follow-up due to Covid-19, felt better and illiteracy (near to half of patients with DRHs were illiterate). Thus, inability to

recall regimens is another important reason associated with increased risk of hospitalization related to failure to receive drugs, as reported elsewhere.[3 11 21]

The second frequent category of DRHs was untreated indication (94, 38.5%) as reported in other studies.[9 22] Reasons were patients remained untreated; prophylaxis and synergistic medications were not indicated. This might be due to incorrect diagnosis; patients didn't come to health setting timely and treating physicians did not follow the management guidelines/protocols. For example, patients having moderate persistent asthma were being treated with albuterol inhalation alone. Statins have not also been prescribed for patients with atherosclerotic cardiovascular disease (ASCVDs) like peripheral arterial disease, stroke, ischemic heart disease and whose age ≥ 40 years with diabetes mellitus and high low density lipoprotein level as per the guidelines. In addition, some compelling indication like hypertension remains untreated and subsequently results in DRHs owing to stroke and others cardiovascular diseases. Furthermore, since only cancer diagnosis and management are carried out in one of this research setting hospital, which is TASH, patients coming from different corners of the country remained untreated and/or treated with various empirical therapies that also lead to improper drug selection until they start anti-cancer drugs in TASH.

ADRs (38, 15.5%) were also commonly reported as the common classifications of DRHs, which is also mentioned with other studies.[11 19-21 29 30 32] This might be associated with numerous number of cardiac and diabetic patients in our study population and poor awareness of patients with regard to cardiac medications untoward effects such as diuretics induced electrolytes disturbance and hypoglycemic symptoms of antidiabetics. Some ADRs could be resulted from failure to follow direction for use of the medications. For example, diabetes mellitus patient who was on metformin experienced epigastric burning sensation pain and vomiting after taking metformin without meal. Overall, the plausible explanations for DRHs might be the absence of pharmaceutical care services

in many health institutions including emergency wards of the study settings, which is very important for optimizing drug therapy and patient safety. There was also poor collaboration among patients, clinical pharmacists and physicians about patient's medications use process involving medications use, their side effects, adherence issue and consequences of not taking their medication properly. Therefore, the better opportunity for clinical pharmacists to add value in patient care roles is through ensuring medication management services according to evidence-based guidelines. In the present study, both failure to receive drugs and untreated indication were reported under the DRPs category of need additional drug therapy that resulted in DRHs, which is supported by other studies.[7 9 18]

In this study, medication classes frequently observed to cause DRHs were cardiovascular medicines, antimicrobial, antineoplastic, endocrine drugs, respiratory medicines and central nervous system drugs. Among these classes of drugs, cardiovascular drug were predominantly involved in DRHs which was in line with other studies.[3 5 6 21 25 27]Cardiovascular drugs, antidiabetics, and antiasthmatics were most commonly associated with DRHs was supported in the previous studies.[2 24 26 27] The most common drugs associated with DRHs mentioned in this study finding were furousemide, ACEIs ,insulins, oral hypoglycemic agents, warfarin, spironolactone ,aspirin and central nervous system agent and these are also implicated in several other studies.[5 7 10 21 22 24 29]The main reason might be connected with the common diseases of the study area which were heart failure, diabetes mellitus, stroke, human immunodeficiency virus and asthma.

Moreover, the most common organ system involved in DRHs was the cardiovascular system (80, 32.6%), with the most common specific disease of heart failure (55, 22.5%) which is consistent with previous studies.[6 25] Moreover, hypertension was mentioned for DRHs which was implicated in the previous study.[5 22 27]This is due to the fact that cardiovascular diseases require multiple

medicine regimens and this contributed to DRPs. Among hospitalized patients attributed to endocrine systems were due to hypoglycemia, hyperglycemia and diabetic ketoacidosis, which are also cited in other studies.[22 27]It might be due to the patients poor awareness about the hypoglycemic symptoms of anti-hypoglycemic agents , poor monitoring control and patients prefer not to take the medications.

In this study, age, educational level and presence of comorbid diseases had statistically significant correlation with the occurrence of DRHs. The findings are consistent with other studies.[18 20 30 33]

In multiple binary logistic regression analysis, patients with ≥ 65 years of age were 7.45 times more likely to be hospitalized due to drug related morbidity than non-drug related as compared to age between 14 and 24 years. This might be owing to age-related physiological changes, larger number of coexisting disease conditions, which require multiple medications and this in turn is associated with an increased risk of DRHs.

From employment factor, students were 6.3 folds high likely exposed to DRHs than non-drug related as compared to the employed. This might be explained by the nature of the disease they had which means students in this finding have majorly contracted heart failure disease secondary to chronic rheumatoid valvular heart disease. Out of a total 16 students, 9 (56.3%) of them had heart failure owing to valvular heart diseases. Consequently, it needs lifelong and multiple medications treatment and then they faced various DRPs leading hospitalizations. Moreover, participants who did not have any occupation were 3.4 times high likely to be hospitalized owing to drug related diseases than non-drug related as compared to employed.

The other factor was education level in which patients with tertiary education level were 64% less likely to be hospitalized with drug related hospitalizations as compared to participants who did not have formal education. This could be related to high level education might be useful to understand

about appropriate medications use. This was supported by the studies conducted at Brasil.[3 11 18] Patients with co-morbid disease were also 2 folds high likely to be drug related hospitalized than non-drug related as compared to patients without co morbid disease. As implicated in the previous studies,[18 30 33] co- morbidity increases the vulnerability towards DRPs. These results clearly indicate the necessity of managing DRHs in multimorbid patients.

In terms of drug related hospital stay, the overall length of the hospital stay in the present study was 4352 days with the average length of hospital stay 10.28±8.99 days, which is longer than what has been reported in other study.[12] This was might be owing to the data in the previous study is in a single hospital and for a relatively short period of time (28 days) while in this finding, the study was carried out at three tertiary care hospitals for the periods of 60 days. Therefore, avoiding preventable DRHs is also a very cost-effective tool for health care systems and could reduce the problem of bed crisis in hospitals.

Among factors which have not demonstrated an association in multivariate analysis, polypharmacy was mentioned. This agree with what have been reported in other studies.[21 25] In contrast, polypharmacy has been reported having positive association with the occurrence of DRHs in previous studies.[3 6 11 21 22 30] This lack of significance could be resulted from variations in number of used medications and identified DRPs for causing DRHs. In this study, around two third of the patients with DRHs used from none to four drugs per patient. Accordingly, to say polypharmacy; ≥ five drugs should be concomitantly taken. Furthermore, the identified DRPs causing DRHs were failure to receive drugs and untreated indication. So, both categories reveal not taking medications and the patients might not use polypharmacy. Additionally; marital status did not illustrate significant association with DRHs.

Conclusion

The prevalence of DRHs was higher than studies conducted elsewhere among emergency ward patients in the study settings. Among those, majority of DRHs were deemed to be preventable. These findings provide valuable insight about category of DRPs and class of drugs that causes DRHs. Age, educational level, participants who did not have any occupation and presence of co-morbid condition have had significant association with DRHs. Hence, researches regarding DRHs should be conducted in different Ethiopian hospitals to demonstrate its impact.

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Contributors

ABB and MBD contributed to conceptualization, design, analysis, and write-up. MBD organized the collection of data for analysis and write up the draft manuscript. ABB and MBD supervised the collection of data and overall research work including interpretation of results, reviewed and revised critically the manuscript. Both authors approved the final version to be submitted for publication.

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Competing interests

There are no conflicts of interest.

Patient consent for publication Not required

Ethics approval

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

Data availability statement

All relevant data are included in the article and uploaded as supporting information files. Extra data are accessed upon reasonable request of the corresponding author.

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

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

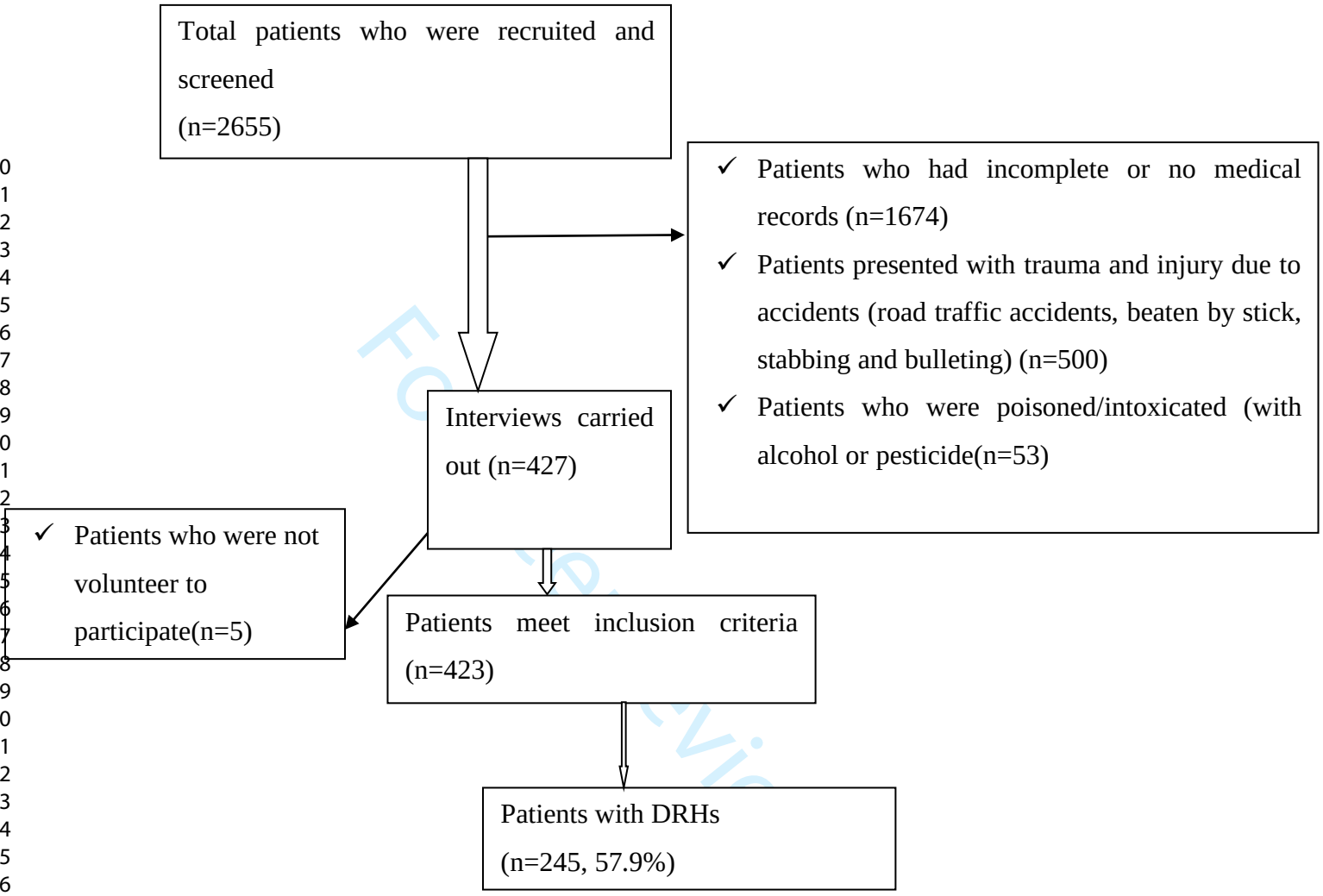

Figure 1

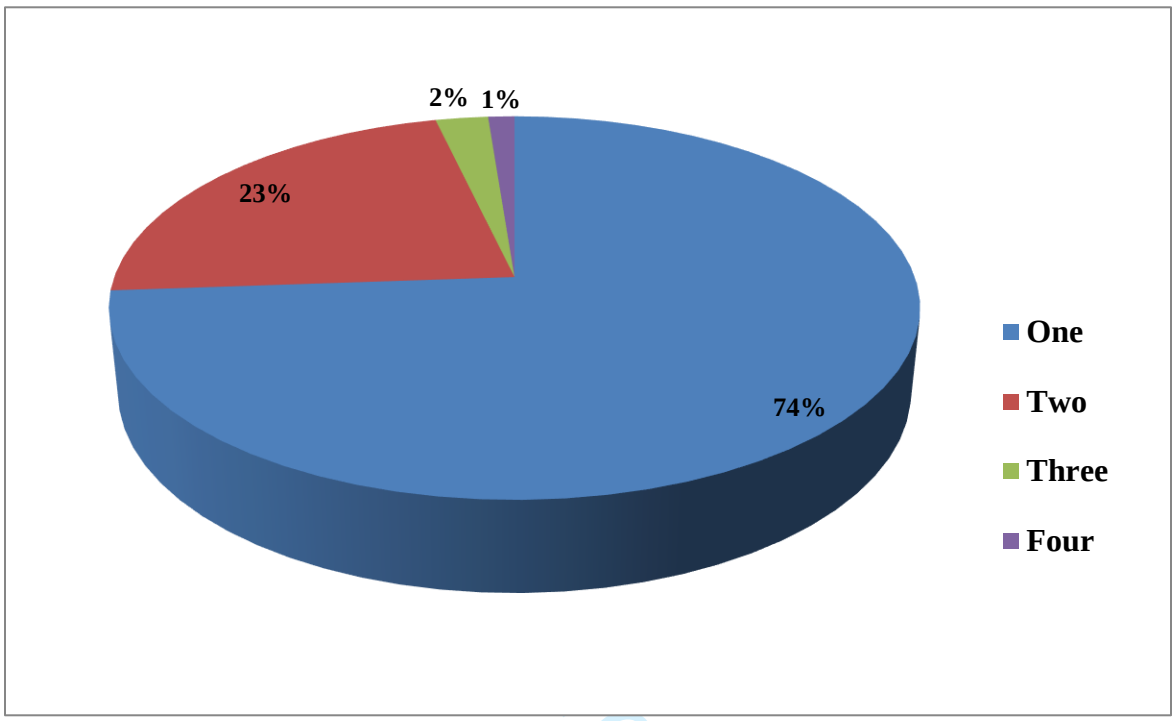

Figure 2