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#### ABSTRACT

Background: Drug related problems (DRP) are common in hospitalized patients and may lead to increase hospital stay, health care cost and augment the risk of morbidity and mortality. Objective: The aim of this study was to assess the prevalence of DRP and associated factors among medical ward patients in University of Gondar teaching hospital (GUH) Methods: A hospital based prospective cross-sectional study was conducted on 256 patients who were admitted in the medical wards from February to April 2016. Data were collected using a pre-tested standard data abstraction format and semi-structured questionnaire. The collected data was checked for completeness and entered into Epi Info 7 software, and analysed using SPSS version 20. Descriptive, binary and multiple logistic regression analyses were used to assess the association between different variables. p<0.05 was used to declare association. Results: Of the 256 study participants, 169 (66.0%) of patients had DRP. A total of 174 DRPs were identified on average of 1.04 DRPs per patient. Of the identified DRP the most common DRPs were found to be due to inappropriate dosage 39.1%, noncompliance 28.9%, and need additional therapy 24.2%. Length of hospital stay [adjusted odds ratio (AOR)=2.416 [95% confidence interval (CI) 1.111-5.253, p=0.028]), number of disease (AOR=3.315 [95%CI: 0.301-36.573], p=0.027) and number of drugs per patient (AOR=9.088 [1.012-81.623], p=0.033) significantly affect DRP. Conclusions: DRPs are common among medical ward patients in

#### **INTRODUCTION**

Even though, medications play a major role in the cure, palliation and inhibition of disease, they also expose patients to drug-related problems (DRPs). According to Pharmaceutical Care Network Europe (PCNE) classification volume 6.2, drug related problems is 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes 'and it is classified them as dosing problems, ADR, drug- drug interaction, inappropriate prescription and patient Adherence to the drug.<sup>[1]</sup>

Previous studies reported that majority of hospitalized patients have some kind of DRPs.<sup>[2-7]</sup> For instance, studies conducted in Norway reported that, 2.6 DRPs occurred per patient in medical ward.<sup>[3]</sup> In addition to this Viktil *et al.* found that the occurrence of DRPs per patient increased linearly with the number of drugs used, with one unit increase in number of drugs yielded 8.6% increase in the number of DRPs.<sup>[8]</sup> Furthermore, a prospective study done in Jordan from medical ward reported that from the total patients, 98.3% had treatment related problems (TRPs) and on average 9.35 TRPs occurred per patient.<sup>[9]</sup>

In many instances, DRPs are a major safety issue for hospitalized patients and it may lead to reduced quality of life, increased hospital stay, increased overall health care cost and even increases risk of morbidity and mortality.<sup>[3]</sup>

There are a number of consequences associated with DRPs which include hospitalizations, long-term care admissions, emergency department visits, additional physician office visits, and additional prescriptions. In addition to these, substantial costs are also associated with DRPs. For example, the economic burden arising from drug related morbidity and mortality in United State of America (USA) was \$177.4 billion annually.<sup>[10]</sup> Whereas, £100707 was reported in

GUH. Inappropriate dosage and unnecessary drug therapy were the top and the least prevalent DRPs respectively. Early identification of DRP and the associated factors to them may enhance the prevention and management of DRPs.

Key words: Drug related problems, drug-therapy problems, inappropriate prescribing, medical wards, Gondar, Ethiopia

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Australian study.<sup>[11]</sup> Therefore, DRPs are major area concern of the patient's physical, psychological and economic burden to the patients as well as to the whole society. Hence, improving drug therapy by preventing drug-related problems may have an important effect on the patients' health, treatment related costs, potentially save lives and enhance patients' quality of life).<sup>[5]</sup>

However, to the best of our knowledge, studies related to DRPs are limited in Ethiopia and no previous research was done in University of Gondar referral Teaching hospital. Like other health Intuitions University of Gondar referral hospital tries to reduce the incidence of DRPs by assigning clinical pharmacists in each ward. However, this effort is not able to control the negative impact of drug therapy problem on the quality of the health service which is provided by this health institution. Therefore, the aim of this study is to assess the extent of DTP and to determine the risk factors associated for the occurrence of DTPs among hospitalized medical ward patients with in this hospital, so the study findings would be used as a base line on epidemiology and potential associated risk factors for DRP in hospitalized medical ward patients in northwest Ethiopia.

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#### **METHODS**

#### Study setting and study population

The study was conducted in University of Gondar teaching hospital (GUH), Gondar, northwest, Ethiopia from February 1, to April 30, 2016. The hospital has 466 beds for inpatient service at five wards. The internal medicine ward is the one among these wards and provides health care services with 2 rooms and 63 beds. The hospital provides primary and referral health care services for nearly 5 million people living in Gondar town and neighbourhood wored as and zones (University of Gondar Teaching Hospital Statics and Information Center, unpublished data, 2015). All Patients admitted to the medical ward, whose age was greater than or equal to 18 years and whose hospital stays were greater than 48 hours (inpatient)were included in the study.

#### Study design and study period

A hospital based prospective cross-sectional study was employed.

#### Variables

Independent variables include demographic characteristics of the patient (age, sex..), number of disease, number of drugs used and duration of hospital stay. The dependent variables were presence of the major types of drug related problems.

#### Sampling technique and sample size determination

The study participants were chosen by using simple random sampling method. The sample size was calculated based on single population proportion formula by assuming that confidence interval=95%, where Za/2 of 95%=1.96, P=73.5% (Because of our source and time limitation we take P=73.5% of Jimma,<sup>[12]</sup> and W=5%.

So, estimated sample size = 
$$\frac{((1.96)^2 \times (0.735) \times (1-0.735))}{(0.05)^2} = 299.299 = 299.$$

Then, corrected estimated sample size  $=\frac{(299.299 \times 1053)}{(299.299 + 1053)} = 233.$ 

Finally, adjusted estimated sample size= $233+(233 \times 0.1)=256$  were included in the study using systemic random sampling technique.

#### DATA COLLECTION PROCEDURE

Data collection was undertaken from February 1, 2016, to April 30, 2016. The clinical information such as patient demographics characteristics, date of admission, date of discharge, lactation and pregnancy status for female, physical examination, diagnostic and laboratory results, current medications, co-morbidities, length of hospital stay, previous medical and medication histories was recorded from patient medical records using data abstraction format which was developed from Pharmaceutical Care Network Europe Foundation Help 1, 29-05-06V 5.01.<sup>[1]</sup>

Additional information and clarifications on some patient's medical information were obtained through discussion with the patient and the physician. To assure the quality of data collection, were a recruited one data collector who is B. Pharm and one supervisor clinical pharmacist (M. Sc) from medical ward; Data collectors and supervisor were trained for two days intensively on contents of medical records, which is valuable to the study, data collection methods and ethical concerns. A pre-test was done on 13 (5%) randomly selected patients' medical records to make sure that whether the study was feasible in this way and to see if the data collection format is appropriate and consistent with the patient medical record while gathering the intended information. After that, necessary modifications were applied to the data abstraction format. The principal investigators were also closely supervising the activity on daily basis. At the end of each data collection day the principal investigator reviewed and checked the completeness and whether recorded information makes sense to ensure the quality of data collected.

#### DATA ENTRY, ANALYSIS AND INTERPRETATION

The collected data were code, cleared and checked for completeness and entered into a computer using Epi Info 7 software and analysed using SPSS version 20. Descriptive statistics was used to characterize drug related problems. Results of the study were organized in the form of frequencies and percentages. The data was summarized and described using tables and figures. Binary logistic regression was used to see the association between independent variable and dependent variable. Those variables with a p value<0.2 in bivariate analysis was a candidate for multivariate analysis and those variables with a p value<0.05 were considered as significant in multivariate analysis. Odds ratio and confidence interval of 95% were used to see the strength of association. Subsequently, the appropriateness of drug therapy was evaluated using 2014 Ethiopian standard treatment guideline for general hospital, Upto-date and world health organization (WHO) guideline. Micromedex drug interaction checker was used to identify drug-drug interactions. Identified DRPs was recorded and classified using DRP registration format which was taken from Pharmaceutical care practice: the clinicians guide.<sup>[13]</sup> Then the possible intervention measures were proposed and communicated to either the internist/resident/senior physician or the patient in order to resolve or prevent DRPs.

#### Ethical clearance

This study was conducted after ethical clearance obtained from the research and ethics review committees of school of pharmacy and the clinical directorate of GUH. The permission to collect data was obtained after official letters were approved by the head of medical ward. All patients in the study were asked for their willingness to participate in the study. Moreover, all other concerned bodies were informed about aim of the study. Besides, to this all the information were collected from the study subjects handled confidentially and data was used for the research purpose only, additionally confidentiality of all the data to be gained were seriously respected.

#### **Operational definitions**

#### Drug related problem

An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.

#### Hospital stay

The time gap spent by the patient in the hospital from his/her admission till his/her discharge (discharge date was determined by looking his/ her discharge date from his/her medical chart).

#### Poly-pharmacy

Use of five or more different drugs concomitantly.

Unnecessary drug therapy

The drug therapy is unnecessary because the patient does not have a clinical indication at this time.

#### Needs additional drug therapy

Additional drug therapy is required to treat or prevent a medical condition or illness from developing.

#### *Ineffective drug therapy*

The drug product is not being effective at producing the desired response or outcome.

#### Inappropriate dosage

The dosage is too low to produce the desired response or outcome or The dosage is too high, resulting in undesirable toxic effects.

#### Adverse drug reaction

The drug is causing any noxious, unintended, and undesired effect, which occurs at doses used in humans for prophylaxis, diagnosis or therapy.

#### Noncompliance

The patient is not able or willing to take the drug therapy as intended.

#### Drug-drug interaction

An interaction is defined as occurring when the effects of one drug are changed by the presence of another drug, food, drink or some environmental chemical agent.

• Within this study drug interactions which are categorized under risk D (i.e., Consider therapy modification) or X (i.e., Avoid combination) was taken as a Drug interaction drug therapy problem.

#### RESULTS

Demographic details and characteristics of patients

During a three month study period a total of 256 patients were included in the study for analysis, of which 144 (56.2%) were females. Majority of patients 114 (44.5%) were in the age group of 18-35 years. A total of 1297 medications were prescribed. Average number of drugs per day for a patient was five. During the hospital stay, majority of the study participant 183 (71.1%) received greater than 5 drugs per day. Demographic characteristics along with other factors that may influence DRPs like number of disease, length of hospital stay, and average number of drugs received per day taken from the medical chart and are presented in Table 1.

The principal diagnoses at admission were confirmed or suspected were infections 124 (48.4%), cardiovascular disease 79 (30.9%), respiratory 76 (29.7%), haematological disease 43 (16.8%), renal and genitourinary disease 23 (9%), endocrine disease 19 (7.4%), gastrointestinal disease 5(2.0%), musculoskeletal and joint disease 5(2.0%), and CNS disorders 4 (1.6%).

#### Prevalence of DRPs

Out of 256 study participants, 169 (66.0%) of patients had DRPs. A total of 174 DRPs were identified on average, 1.03 DRPs per patient. From the total DRPs, one DRP was identified in 140 (54.7%) patients, two DRPS in 33 (12.9%), and more than 2 DRPs in 1(0.4%) patient. From the studied DRPs, most highly reported DRP was found to be due to inappropriate dosage 39.1%, non-compliance 74 (28.9%), followed by need additional therapy 62 (24.2%). The types and number of drug related problem identified are summarized in Figure 1.

### Drugs and drug classes involved in drug related problems (DRPs)

Commonly prescribed drug classes were anti-infective 192 (75%), Gastro intestinal drugs (GI) 92 (35.9%), Cardiovascular system (CVS) drugs 84 (32.8%), and drugs for blood disorder 87 (34%) [Table 2].

A total of 59 drugs were involved in different types of DRPs and the most common agents associated with drug therapy problems were omeprazole 45 (17.6%), heparin 22 (8.6%), and aspirin 21 (8.2%). The common drugs associated with the major types of DRPs and drug-drug interaction are shown in Table 3.

 
 Table 1: Socio demographic characteristics and clinical data of admitted medical patients in UoGTH, from February 1 to April 30, 2016 (N=256)

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Demographic characteristics and clinical data	Category	Frequency	Percent (%)
Sex	Male	112	43.8
	Female	144	56.2
Age group	18-35	114	44.5
	36-64	104	40.7
	≥ 65	38	14.8
Hospital stay	< 7	53	20.7
	≥ 7	203	79.3
Number of diseases	1	60	23.4
	2	113	44.1
	3	58	22.7
	4	16	6.3
	≥ 5	9	3.5
Number of drugs prescribed	< 5	73	28.5
	5-9	166	64.8
	≥ 10	17	6.3

Table 2: Common drug classes involved in drug related problems

S. No.	Drug class	Frequency	Percent
1	Anti-infective	192	75
2	Gastrointestinal drugs	92	35.9
3	Cardiovascular drugs	87	34
4	Drugs for blood disorder	84	32.8
5	Analgesics and antipyretics	77	30.1
6	Anti-inflammatory and glucocorticosteroid	51	19.9
7	Central nervous system drugs	26	10.2
8	Endocrine drugs	15	5.9
9	Vitamins	14	5.5
10	Respiratory drugs	11	4.3

**Table 3:** Top 10 drugs which are associated with the occurrence of DRPs among admitted medical patients in GUH from February 1 to April 30, 2016 (N=256)

S. No.	Drug	Frequency	Percent
	Omeprazole		
1	Heparin	52	19
2	Ceftriaxone	22	8.2
3	Vancomycin	15	5.6
4	Refampicn, isoniazide, pyrazinamide	12	4.5
5	And ethambutol combination	12	4.5
6	Cotrimoxazole	11	4.1
7	Potassium chloride	9	3.4
8	Atorvastatin	8	3
9	Warfarin	8	3
10	Furosemide	7	2.6

#### Intervention for DRP

Suitable intervention was taken to correct the identified DRPs. The majority of DRPs (55%) interventions were given by the investigators and physicians. The most commonly practical interventions was informing the physician to change the dose, add drugs and educate their patient to enhance the compliance.

#### Factors associated with DRPs

Independent factors which predicted the occurrence of DRPs in the study population were sex, age, average number of drugs/day, length of hospital stay and number of disease, poly pharmacy, and clinically significant potential drug-drug interactions, were analysed to

determine whether they could predict the occurrence of DRPs or not.

The result of the binary logistic regression showed that association was observed between sex (p=0.003), age (p=0.000), length of hospital stay (p=0.000), number of disease (p=0.027), and number of drugs per patient (p=0.007) with the presence of DRPs.

Perceived associated factors (i.e., sex, age, hospital stay, number of disease, and number of drugs per patient) which were found to be significant by binary regression, were introduced to multiple logistic regressions (i.e., by considering p<0.2).

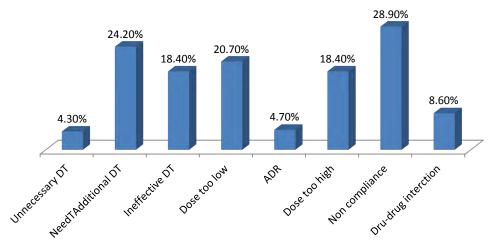
The result of the multinomial logistic regression showed that association was observed between length of hospital stay (p=0.028), number of disease (p=0.027) and number of drugs per patient (p=0.033) with the presence of DRPs. Patients who took an average of 5-9 drugs per day are 9 times more likely to develop drug related problem as compared to patients who took less than 5 drugs per day (AOR=9.088 [1.012-81.623]). Patients whose hospital stays was greater than seven days, were 2.416 times more likely to have DRPs than patients whose hospital stay less than seven days (AOR=2.416[1.111-5.253]). Patient who have 2 or more number of disease were 3.315 times more likely to have DRPs

than patients who have single disease AOR 3.315[0.301-36.573] [Table 4].

#### DISCUSSION

The incidence of DRPs among hospitalized patients is associated with different reasons and risk factors. Identifying these factors is critical for the prevention and control of DRPs in an individual patient. This study was employed to assess DRPs in medical inpatients of among the tertiary care teaching hospital in Ethiopia.

The current study showed that a total of 174 drug related problems were identified of these DRP was in 140 (54.7%) patients, 2 DRPS in 33 (12.9%), and more than 2 DRPs in 1 (0.4%) patient. This finding was lower than with those similar studies done in India in which, 1 DRP was found in 33 (67.4%) patients, 2 DRPS in 12 (24.5%) patients and 3 DRPs in 4 (8.2%) patients,<sup>114]</sup> Addis Ababa, Ethiopia<sup>[15]</sup> in which DRP was identified in 82 (70.1%) patients, 2 DRPS in 31 (26.5) patients and more than 2 DRPs in 4 (3.4%). However the result of this study was higher compared with a similar study done in Jimma, Ethiopia in which a single DRP was identified in 97 (37.7%) of patients.<sup>[12]</sup> This may be due to the reason that more clinical pharmacists were involved in the ward based activities in GUH.



**Figure 1:** Percentage of specific Type of drug related problems identified among admitted medical patients in GUH, from February 1 to April 30, 2016 (N=256) **Table 4:** Binary and multinomial logistic regression result of factors associated with DRPs in medical wards of GUH from February 1 to April 30, 2016 (N=256)

Variable	Category	DRP	DRP (%)			Develop
		Yes (%)	No (%)	COR (95%CI)	AOR (95%CI)	P-value
Sex	Female	77(45.6)	67 (77)	1.147 (0.681-1.929)	0.923 (0.476-1.790)	0.813
	Male	92 (55.4)	20 (23)	1.000*	1.000*	
Age group	18-35	64 (37.9)	50 (57.4)	0.340 (0.166-0.694)	2.240 (0.930-5.392)	0.072
	36-45	72(42.6)	32(36.8)	0.822 <b>(</b> 0.322-2.104 <b>)</b>	1.023 (0.335-3.124)	0.968
	≥ 65	33 (19.5)	5 (5.8)	1.000*		
Hospital stay	<7	24 (14.2)	29 (33.3)	1.000*	1.000*	
	≥ 7	145 (85.8)	58 (66.7)	0.331 <b>(</b> 0.178-0.616 <b>)</b>	2.416(1.111-5.253)	0.028**
	1	25 (14.8)	35 (40.2)	0.220 <b>(</b> 0.027-1.818 <b>)</b>	1.263 (0.119-13.418)	0.160
Number of disease	2	72 (42.6)	41 (47.1)	0.089 <b>(</b> 0.010-0.76 <b>)</b>	3.315(0.301-36.573)	0.027**
	3	49 (29)	9 (10.3)	0.681 (0.076-6.124)	0.564 (0.049-6.528)	0.731
	4	15 (8.9)	1 (1.1)	1.875 <b>(</b> 0.103-34.131 <b>)</b>	1.063 (0.045-25.178)	0.671
	≥ 5	8 (4.7)	1 (1.1)	1.000*	1.000*	
Number of drugs prescribed	<5	71 (42.0)	2 (2.3)	2.219 (0.189-25.995)	0.313 (0.024-4.011)	0.399
	5-9	82 (48.5)	84 (96.6)	0.061 (0.008-0.471)	9.088 (1.012-81.623)	0.033**
	≥ 10	16 (9.5)	1 (1.1)	1.000*	1.000*	

Note: COR-crude odds Ratio; AOR-adjusted odds ratio; \*Significant at 0.05; \*\*Significant; 1\*- Constant

The finding of this study show (66.0%) of patients admitted to medical ward within the study period had DRPs. This finding is higher than what was found in Addis Ababa, Ethiopia (52%) this might be due to the consideration of non-compliance in our study.<sup>[15]</sup> However, this finding was lower than with those similar studies done in Jimma, Ethiopia (73.5%),<sup>[12]</sup> Adama, Ethiopia (80.7%),<sup>[16]</sup> Norway (81%),<sup>[4]</sup> Malaysia 90.5%<sup>[17]</sup> and Jordan (98.3%).<sup>[9]</sup> The lower rate of DRP in this study as compared to what was done in Jimma might be because the data collection of the study in Jimma was conducted at 2011 when clinical pharmacists were not involved in the ward based activities. The study in Malaysia also found a prevalence of 90.5%.<sup>[17]</sup> The lower prevalence of DRPs in our study as compared to the Malaysian study might be because that the Malaysian study was done on patients with type 2 diabetes mellitus and hypertension. These patients have a higher probability to develop DRP since patients with diabetes and hypertension are more prone to receive more drugs and to develop more complications.

In the present study inappropriate dosing (dose too low and dose too), noncompliance, need additional drug therapy; and ineffective drug therapy were most frequently encountered DRPs. The finding of this study showed that inappropriate dosage was 39.1% (dose too low (20.7%) and dose too high (18.4%)). This finding was consistent with those similar studies done in Norway, 35.1%,<sup>[4]</sup> Jimma, 29.4% (15.5% high medication dosage and low medication dosage in 13.9%)<sup>[12]</sup> and India (25.4%).<sup>[14]</sup> However the result of this study was significantly higher when compared to a similar study done in Addis Ababa (10.5%). <sup>[15]</sup>

This finding showed that non-compliance was the second most prevalent DRPs 28.9%. This result is comparable with a study done in Adama Hospital Medical College, East Ethiopia<sup>[16]</sup> in which non-adherence was the second most prevalent DRP next to drug interaction. However, this result is in contrast with that similar study done in Jimma, 9.8%.<sup>[12]</sup>

In this study need of additional drug therapy was 24.2%. This study is inline with the study done at Jimma 32.6%.<sup>[12]</sup> However lower than what was found in Addis Ababa (11.8%).<sup>[15]</sup> The least prevalent drug related problems in the present study were adverse drug reaction (ADR), 3% and drug interaction, 7% respectively. This finding not in line with similar study done in Addis AbebaADR 23% and drug interaction 48%<sup>[15]</sup> and India ADR (12.7%), drug interaction (21.1%).<sup>[14]</sup>

This study showed that the average number of drugs taken by the patient/day, number of disease and length of hospital stay were shown to be a risk factor for the occurrence of DRPs. In the present study number of drugs were significantly associated with DRPs. Patients who took an average of 5-9 drugs per day are 9 times more likely to develop drug related problem as compared to patients who took less than 5 drugs per day(AOR=9.088 [1.012-81.623]. This finding is in agreement with those studies done in Tiku rAnbessa, Addis Ababa,<sup>[15]</sup> Adama, Ethiopia,<sup>[16]</sup> and oncology unit in Tiku rAnbessa specialized Hospital, Addis Ababa,<sup>[18]</sup> Norway,<sup>[4]</sup> and Jordan,<sup>[9]</sup> in contrast to this a study done in Jimma University Specialized Hospital.<sup>[9]</sup>

In this study, patients whose hospital stay was greater than seven days, were 2.416 times more likely to have DRPs than patients whose hospital stay less than seven days (AOR=2.416 [1.111-5.253]). This result was not in consistent with those studies done in Addis Ababa.<sup>[15]</sup> The finding of this study showed that, patient who have 2 or more number of disease were 3.315 times more likely to have DRPs than patients who have single disease AOR 3.315 [0.301-36.573]. This finding was consistent with the study done in Jimma,<sup>[12]</sup> however, in contrast with the study done in Addis Ababa.<sup>[15]</sup> However, in the current study sex and age did not have significant correlation with the occurrence of DRP. This result is in line with similar studies.<sup>[4,9,19]</sup>

In this study anti-infective, GI medicines and central nervous system (CNS) drugs were common drug classes involved in DRP. The study on DRPs at Jimma university specialized hospital, Ethiopia found antimicrobials were the top ranking drug classes involved in drug related problems.<sup>[12]</sup> Another study in France indicated anti-infective and CNS drugs were from the top 3 drug classes involved in DRP.<sup>[20]</sup>

This study showed that most common agents associated with drug therapy problems were omeprazole, heparin, ceftriaxone, vancomycin, RHZE, cotrimoxazole, warfarin, atorvastatin, potassium chloride (KCL), and furosemide. This is similar with the a study conducted in Medical Wards of TikurAnbessa Specialized Hospital, Addis Ababa, Ethiopia were heparin, prednisolone, and warfarin found to be were the top ranking drugs involved in DRP.<sup>[15]</sup>

#### Limitations of the study

DRPs related to medication administration were not addressed in the study. The result of the study may not be generalized to all hospitals because it was single centred study conducted in a hospital serving referred patients who have severe illnesses and more co morbidities.

Finally, because our study involved patients admitted to medical service generalization of the results to other services (i.e., surgery ward, paediatrics ward etc.) may be limited. Further research is warranted to determine the most commonly implicated drugs and risk factors associated with drug-related hospitalizations in other hospitalized populations, patients living in the community, and nursing home residents.

#### **CONCLUSION**

The present study indicated that DRPs are common among medical ward patients. Noncompliance and unnecessary drug therapy were the top and the least prevalent DRPs respectively. The most common drug classes involved in DRP were anti-infective, GI medicines, CNS drugs and medicines affecting the blood. Omeprazole and heparin were the most common agents associated with drug therapy problems. The risk factors associated with the presence of DRPs were number of medications, number of diseases and length of hospital stay.

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#### Author Contributions

All authors were involved in proposal writing, data analysis and interpretation; write up of the final research and manuscript preparation and finalization.

#### Disclosure

The authors have no conflicts of interest that are directly related to the content of this study.

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None.

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