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RESEARCH ARTICLE

Preventability analysis of adverse drug reactions in a Jordanian hospital: a prospective observational study

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Abstract

Background Adverse drug reactions remain to be an issue that compromise patient's safety in Jordan and worldwide. In Jordan, an assessment of factors involved in preventability of adverse drug reactions has not been conducted previously. *Objectives* To describe the proportion of preventable adverse drug reactions, and the causes of hospital-related preventable adverse reactions in one Jordanian hospital. *Methods* A prospective observational study of 4 months duration conducted by clinical pharmacists in the hospital. *Setting* Surgical and medical wards in one Jordanian private hospital. *Main outcome measure* Proportions of admissions related to adverse drug reactions, proportions of preventable reactions and analysis of the factors involved in the preventable adverse drug reactions. *Results* Out of 350 admissions recorded during the study period, a total of 38 (10.8%) adverse reactions were detected. Among those, 29 (8.3%) were detected in the hospital and 9 (2.6%) were the cause of the hospital admission. Many (44.7%) of the adverse drug reactions were preventable (31.6% were probably preventable and 13.1% were definitely preventable). About half (55.3%) were unpreventable. Insufficient monitoring was involved in 29.4% of the preventable adverse reactions and inappropriate dosing and drug–drug interactions were independently responsible for 17.6% of the preventable adverse reactions. *Conclusion* A high proportion of the identified adverse drug reactions were found to be preventable. Insufficient monitoring and inappropriate dosing were the most important factors associated with preventable adverse drug reactions. Nationally, more focused efforts need to be stimulated to prevent preventable adverse drug reactions in hospitals.

Keywords Adverse drug reactions · Hospital · Jordan · Preventability analysis

Impacts on practice

- Findings can lead to improvements in patients' safety and health outcomes by reducing moralities and morbidities associated with identified ADRs
- Identified ADRs can help focused efforts on a national level to enhance preventability of ADRs in hospitals

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Introduction

Adverse drug reactions (ADRs) have been defined as an unintended noxious response occurring at doses normally used in patients detected after the use of drugs for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function (WHO) [1]. According to the Rawlins–Thompson system, ADRs can be divided into two main groups: Type A and Type B. Type A ADRs are the normal, but quantitatively exaggerated pharmacological effects of a drug; for example, bradycardia caused by the use of β-blockers such as propranolol. Type B ADRs are considered as qualitatively abnormal effects of drugs, which appear to be unrelated to the drug's normal pharmacology such as immunological reaction caused by penicillin [2].

ADRs are regarded to be a troublesome outcome at both economic and human levels. For humans, ADRs can lead to significant morbidities and mortalities and thus it could compromise patient safety. Serious outcomes include

hospital admission, prolonged hospitalization, irreversible illnesses, pathological conditions, disabilities and even death [3]. Therefore, choosing a particular medicines regimen, patient safety should be taken into consideration by checking patient's susceptibility to ADRs. Some of the factors that could affect patient susceptibility to ADRs include: age, gender, ethnicity, genetic variations, kidney and liver functions, comorbidities, polypharmacy, drug dose and frequency. In addition, choosing a particular medicine regimen, effectiveness should be taken into consideration [4, 5]. Economically, ADRs could have a huge financial burden. A prospective clinical study of ADRs monitoring in France, ADR-induced cost due to the prolongation of length of hospital stay was evaluated to be 4150 Euro per ADR per patient [6].

ADRs are commonly recognized in hospital setting due to the fact that some of these reactions were the reason for hospitalization. Many previous prospective studies were conducted all over the world to estimate the incidence of ADRs leading to hospitalization. A review of epidemiological studies quantifying ADRs in European settings between 2000 and 2014 found that the median percentage of hospital admissions due to an ADR was 3.5%. In addition, the incidence of patients who experienced an ADR during hospitalization was 10.1% [3]. The Jordanian Food and Drug administration (JFDA) has recommended that all serious or unusual suspected ADRs must be reported [7], yet there is no systematic continuous reporting of ADRs followed by Jordanian hospitals affiliated to JFDA.

Clinically, the most important aspect of ADRs would be their preventability. This would dramatically decrease the incidence of the morbidities and mortalities encountered. According to previously conducted studies in the hospital setting all around the world, the preventability of drug related admissions ranged from 38 to 68%, depending on the type of the method used for identify ASRs; e.g. prospective versus retrospective, the country in which the study was conducted, and the differences in setting and population [8–11]. Preventable adverse events during the hospital stay ranged from 16 to 61% [12–14]. Data in Jordan are limited, with two observational cross sectional studies conducted at Al-Karak Teaching Hospital that reported 50% and 25% of ADRs respectively which were preventable [15, 16]. Given the moderate to high percentages for the preventability of ADRs in the literature and the lack of Jordanian studies investigating the most identifiable factors and reasons for ADRs preventability, this study was conducted to explore the situation of such an important issue.

Aim of the study

Two primary objectives were set for this study; first to describe the proportion of the preventable hospital-related ADRs including those which occurred during hospitalization, ADRs reported at admission but were not the reason for hospitalization, and ADRs that have caused the hospital admission. Secondly, to describe the causes and factors involved in the preventability of ADRs including the proportions of hospital-related ADRs, their clinical characteristics, severity and most frequent classes of medications suspected to cause the identified ADRs.

Ethics approval

The research proposal and protocol have been submitted and reviewed by an independent review committee (IRC) at the Ministry of Health. Approval has been given from the IRC of the Ministry of Health (reference no. 170147/2017). Following the Ministry of Health's approval, the hospital's management permission to conduct the research was granted.

Methods

This prospective observational study was conducted over 4 months (mid January 2018 to mid May 2018) in a 250 bed hospital in Amman, Jordan. Patients who were admitted into the hospital medical and surgical wards were evaluated for enrolment in the study. Inclusion criteria included: patients who were above the age of 18 years (this was based following two previous studies which excluded children) [8, 10], also patients who have been taking at least one medication during hospitalization and admitted to the wards for at least 24 h (this was based on a previous publications) [17]. Patients admitted due to ADRs were also included in the study. On the other hand, patients who were considered a day case (admitted 24 h or less) and did not receive any medications during hospitalization or who were admitted to the Cardiac Care Unit (CCU), Intensive Care Unit (ICU) and emergency department were excluded from the study. A prospective observational clinical surveillance for patients included in the study was conducted by a trained clinical pharmacists working on wards (observers). The observers were consisted of four trained clinical pharmacists working at the hospital and the main researcher (a clinical pharmacist who is the principal investigator of the study (PI)). Training of the clinical pharmacists consisted of a patient safety presentation (including detailed information about ADRs identification and reporting), presentation describing the study methods and a relevant literature review. The PI underwent a practice case report generation for 4 weeks before starting the study supervised by the senior researcher of the study.

For each patient admitted during the study period, a form has to be completed of patient age, gender, admission diagnosis, co-existing diseases, home medications, currently prescribed drugs in the hospital, daily doses, indications for each drug and duration of hospitalization (Appendix 1).

Daily screening of ADRs were then conducted by the PI using "review of a system" form (Appendix 2) which utilized patients' interview (the subjective part) and objective measurements such as laboratory values, vital signs, physical examinations and other diagnostic means such as imaging (extracted from medical records). If necessary, additional case discussions with the treating physicians were performed. Data used in both Appendices 1 and 2 have been extracted from previous similar study [9]. Patients were also interviewed by the PI to retrieve info that helped in confirming the ADRs (See Table 1 on Naranjo Algorithm). The PI introduced herself as a clinical pharmacist working at the hospital and performing an assessment of patients' treatment records in order to improve the service delivered. The other clinical pharmacists working at the hospital (n = 4) reported the suspected ADRs to the PI.

All suspected ADRs diagnoses were taken from physician notes found in patients' medical records. They were coded using the International Classification of Diseases (ICD-10) [18], and the drugs were coded according to the Anatomical Therapeutic and Chemical codes [19]. ICD-10 provided a code and formal categorizations for the systems affected by ADRs. The affected systems determined using ICD-10 were: diseases of the blood, diseases of the digestive system, Endocrine, nutritional and metabolic diseases, diseases of the respiratory system, diseases of the skin and subcutaneous tissue, diseases of the genitourinary system, diseases of the musculoskeletal system and connective tissue and diseases of the nervous system.

For each suspected ADR, causality, preventability and severity analysis were conducted. For causality evaluation, the suspected ADRs were assessed by the clinical pharmacist using the Naranjo Algorithm. This was designed by Naranjo et al. [20] for determining whether a suspected ADR is actually caused by the drug, as opposed to other factors using a set of questions. According to the algorithm, the probability that the adverse event was related to drug therapy was classified as definite, probable, possible, or doubtful. 'Definite" reaction is chosen if a) it followed a reasonable temporal sequence after a drug intake or in which a toxic drug level had been established in body fluids or tissues, b) followed a recognized response to the suspected drug and c) confirmed by improvement on withdrawing the drug and reappeared on re-exposure. A "probable" reaction if a) it followed a reasonable temporal sequence after a drug intake, b) followed a recognized response to the suspected drug, c) confirmed by withdrawal but not by exposure to the drug, and d) could not be reasonably explained by the known characteristics of the patient's clinical state. A "possible" reaction if a) it followed a temporal sequence after a drug intake, b) followed a recognized pattern to the suspected drug and c) could be explained by characteristics of the patient's disease. A reaction was defined as "doubtful" if it was likely related to factors other than the drug. Other questions used in the Naranjo Algorithm, including "did the adverse event appear after the drug was administered and did the adverse event improve when the drug was discontinued (If the adverse event was subjectively evaluated), and did you have a similar reaction to same or similar medications in any previous exposure" were asked to the patients during the interview. Patients had the choice to answer these questions with yes, no, or don't know. Questions used in the Naranjo Algorithm are illustrated in Table 1 [20].

The clinical pharmacists also performed a severity assessment for the identified ADRs using Hartwig's Severity Assessment Scale. Accordingly, ADRs were classified into mild, moderate and severe. Criteria used to determine ADRs severity according to Hartwig's scale are illustrated in Table 2 [21].

For preventability analysis, definite, probable and possible ADRs were included. Preventability analysis was conducted using modified Schoumock and Thornton scale

Table 1 Questions included in the Naranjo Algorithm used for adverse drug reactions (ADRs) causality assessment [20]

Questions	Yes	No	Don't know
1. Are there previous conclusive reports on this reaction	+1	0	0
2. Did the adverse event appear after the drug was administered	+2	−1	0
3. Did the adverse event improve when the drug was discontinued or specific antagonist was administered	+1	0	0
4. Did the adverse event reappear when the drug was re-administered	+2	−1	0
5. Are there alternative causes (other than the drug) that could have caused the reaction	−1	+2	0
6. Did the reaction reappear when the placebo was given	−1	+1	0
7. Was the drug detected in the blood (or other fluid) in concentration known to be toxic	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased	+1	0	0
9. Did the patient have similar reaction to the same/similar drugs in any previous exposure	+1	0	0
10. Was the adverse event confirmed by any objective evidence	+1	0	0

Definite > 8, probable 5–8, possible 1–4, doubtful = 0

Questions asked to patients during patients' interview. Questions 2 and 3 only asked if adverse drug reaction was subjectively evaluated

Table 2 Hartwig's scale showing criteria and matched levels used for adverse drug reaction (ADR) severity assessment [21]

Level	Criteria
Mild (level 1)	The ADR requires no change in the treatment with the successful drug
Mild (level 2)	The ADR requires the suspected drug be withheld, discontinued or otherwise changed No antidote or other treatments required and there is no increase in length of stay
Moderate (level 3)	The ADR requires the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatments required with no increase in length of stay
Moderate (level 4)	Any level 3 ADRs that increases the length of stay by at least 1 day or was the reason of admission
Severe (level 5)	Any level 4 ADRs that requires intensive medical care
Severe (level 6)	The ADRs causing a permanent harm to the patient
Severe (level 7)	The ADRs directly or indirectly leading to the death of the patient

ADR adverse drug reaction

which classifies ADRs into definitely preventable, probably preventable and non-preventable ADRs. The clinical pharmacists also performed an analysis involving the factors and causes regarding preventable ADRs. Further analysis involving the preventability and the causes for the three categories of ADRs were classified as follows: ADRs detected upon admission but were not the reason for hospitalization, ADRs that were the primary reason for hospitalization, and ADRs that happened during hospitalization (were not present upon admission but rather developed during hospitalization). Modified Schoumock and Thornton criteria for preventability analysis are illustrated in Table 3 [22].

Decisions regarding the causality, severity and preventability of ADRs were agreed upon with all the clinical pharmacists attending the medical and surgical wards (n = 4) and the PI according to the criteria described above through regular meetings. In case of any disagreement, the decision was made based on the decision of the majority of clinical pharmacists. For each ADRs category, a complete data consisted of Appendices 1 and 2 along with the agreed upon decision of causality, severity and preventability were prepared (manual database). The validated collected database was then imported into the study database by the PI.

Data was analysed using Statistical Package for Social Sciences (SPSS) version 21 (Chicago, Illinois). Differences with p value of $< 5\%$ were considered statistically significant. Appropriate analysis was used depending on the variable type, normality assessment and function required. The Kolmogorov–Smirnov Test was used for normality assessment. For continuous variables, independent sample t-test was used, while Chi square test was used for categorical variables. Correlation analyses were performed using Pearson's correlation to identify relationships between the rate of ADRs occurrence and patient age, length of stay, number of medications and number of co-morbidities.

Results

Characteristics of patients and their risk factors for ADRs occurrence

Out of 350 admissions (330 patients) recorded during the study period, a total of 38 (10.8%) ADRs were detected (Fig. 1). These 38 ADRs have occurred in 31 patients, 15 (48.4%) were males and 16 (51.6%) were females. Their mean age was 63.3 years, mean length of stay was 6.8 days,

Table 3 Modified Schoumock and Thornton scale showing questions used in the assessment of preventability category for adverse drug reaction (ADR) [22]

Definitely preventable
Was there a history of drug allergy or previous reaction to the drug?
Was the drug involved inappropriate for patient clinical condition?
Was the dose, rout or frequency of administration inappropriate for the patient age, weight or disease status?
Probably preventable
Was a therapeutic drug monitoring or other necessary laboratory tests not performed?
Was a drug interaction involved in ADRs?
Was poor compliance involved in ADRs?
Was preventive measure not prescribed/administered to the patients?
Not preventable
If all above criteria not fulfilled

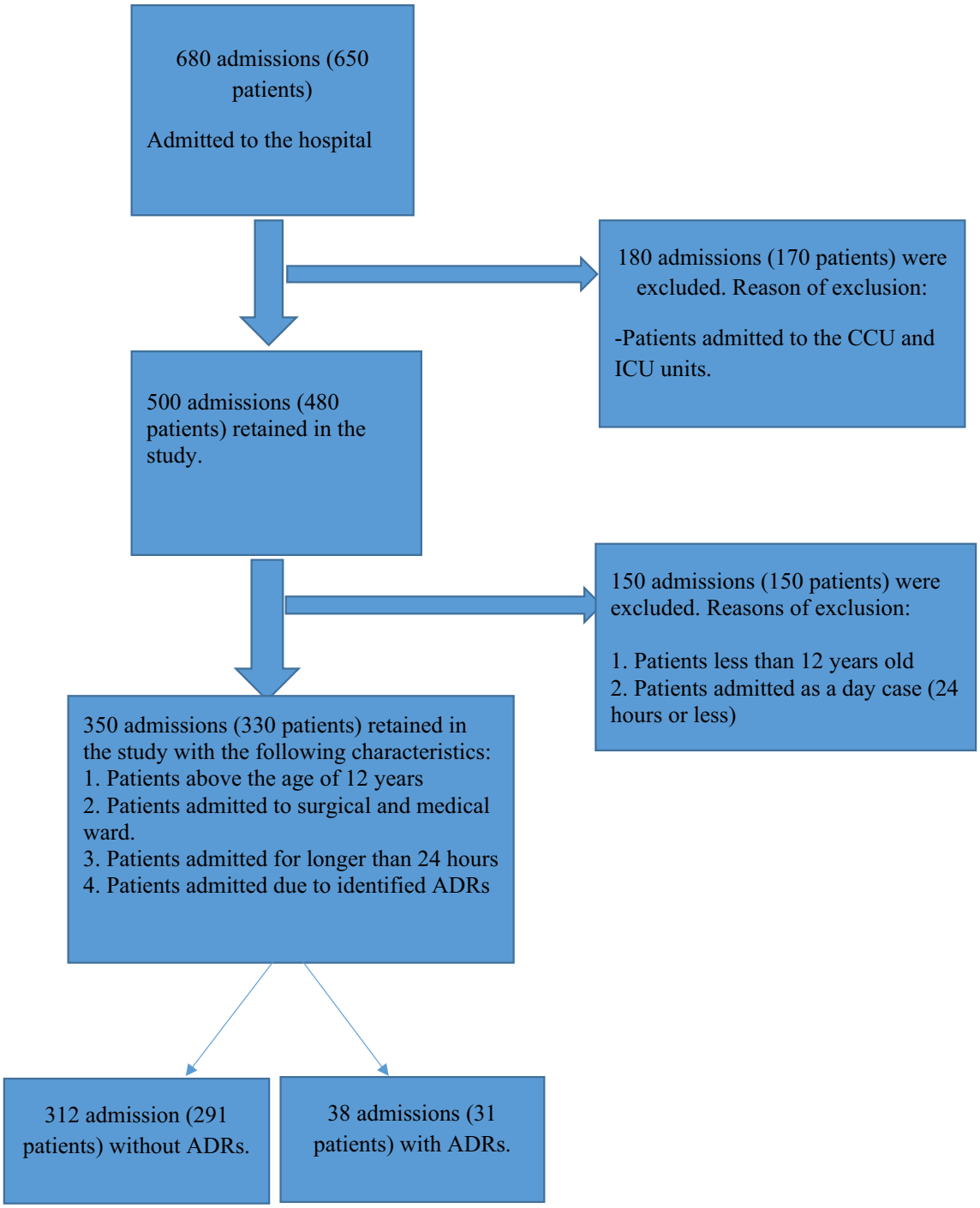

Fig. 1 Study diagram showing patients recruitment and retainment in the study

mean inpatient medication number was 7.1 medications and the mean number of co-morbidities was 2.6 medical conditions.

Risk factors for ADR occurrence include; age, polypharmacy, co-morbidities and longer length of hospital stay. There was a significant statistical difference between the patients with or without ADRs in age ($p = 0.002$), length of stay ($p = 0.01$) and number of co-existing conditions or co-morbidities ($p = 0.001$). Patients with no ADRs were younger, hospitalized for shorter periods of time and had fewer co-morbidities. However, there was no statistical difference in gender or the number of medications prescribed between the two groups.

Types of ADRs, classes of medications involved and effects on body systems

Among the 38 ADRs detected during the study period, 25 (65.8%) ADRs were classified to be type A, while 13 (34.2%) were classified as type B. According to the ATC classification, ten classes of medications were responsible for the identified ADRs. Out of these classes, four were the most frequently occurring, including 11 cardiovascular agents (28.9%), 7 anti-thrombotic agents (18.4%), 5 anti-infective agents and 5 from drugs working on the musculoskeletal system (13.2%) of the ADRs. The remaining six classes included systemic hormonal agents, immunosuppressants, diagnostic agents, drugs working on the nervous system, drugs working on the respiratory system and drugs working on the alimentary tract.

Identified ADRs in our study affected mostly the endocrine system and metabolism (10; 26.3%), the hematological system (9; 21.1%), dermatological system (6; 15.8%) and the gastrointestinal system (4; 10.5%). Other systems include renal, hepatic, cardiovascular, respiratory and neurological systems. A detailed description of adverse drug reactions, affected systems and drugs involved are presented in Table 4.

Causality, preventability and severity descriptions

Out of a total of 38 (10.8%) ADRs reported during the study period, 29 were detected in the hospital (8.3%) and 9 were the cause of patients' hospital admissions (2.6%). The 38 ADRs were further analyzed for causality, preventability and severity. According to the Naranjo algorithm, 32 of the ADRs were probable (84.2%) and 6 were possible (15.8%). None of the detected ADRs were definite. According to Hartwig's Severity Assessment Scale, 17 of the ADRs were mild (44.7%), 20 were moderate (52.6%) and only 1 was severe (2.6%) requiring an intensive medical care intervention.

According to the modified Schumock and Thornton scale, 17 were considered preventable ADRs (44.7%) among them 5 were "definitely preventable" (13.1%) and 12 were "probably preventable" (31.6%), while the remaining 21 were "non-preventable" (55.3%) (Fig. 2).

Among the 38 ADRs detected during our study period, 18 reactions occurred during hospitalization (47.4%), of which 4 were deemed to be preventable (22.2%), 11 were present at admission (28.9%), but were not the reason for admission, among them 8 were deemed to be preventable (72.7%). The remaining 9 patients were due to hospitalization 9 (23.7%), of which 5 reactions were deemed preventable (55.5%) (Fig. 3).

Table 4 The different affected systems and drugs involved for the adverse drug reactions (ADRs) detected in the study

Affected system	Adverse drug reactions	Drugs involved
Endocrine and metabolic	Hyperkalemia	Spironolactone, Candesartan
	Hypokalemia	Torsemide, furosemide, prednisone
	Hyponatremia	Hydrochlorothiazide
	Hyperglycemia	Methylprednisolone
Hematological (blood)	Thrombocytopenia	Enoxaprin
	Neutrophilia	Prednisone
	Leukopenia	Azathioprine
	Hematuria	Apixaban
	Ecchymosis	Clopidogrel
	Hematoma	Warfarin/enoxaparin
	Epistaxis	Warfarin
	Hematemesis	Warfarin
	Melena	Warfarin
Dermatological (skin)	Toxic epidermal necrolysis	Ibuprofen
	Urticaria/hives	Contrast media
	Skin rash	moxifloxacin, diclofenac, rituximab
		Allopurinol
Digestive system	Diarrhea	Imipenem
	Gastric ulcers	Aspirin/prednisone
	Vomiting/Nausea	Tigecycline
	Acute asymptomatic rise in ALT and AST	Tecioplanin, quetiapine
Genitourinary system (renal)	Acute kidney injury	Vancomycin, furosemide
Respiratory	Pulmonary fibrosis	Amiodarone
Nervous system	Somnolence	Levodopa/carbidopa

PT prothrombin time, *ALT* alanine amino transferase, *AST* aspartate amino transferase

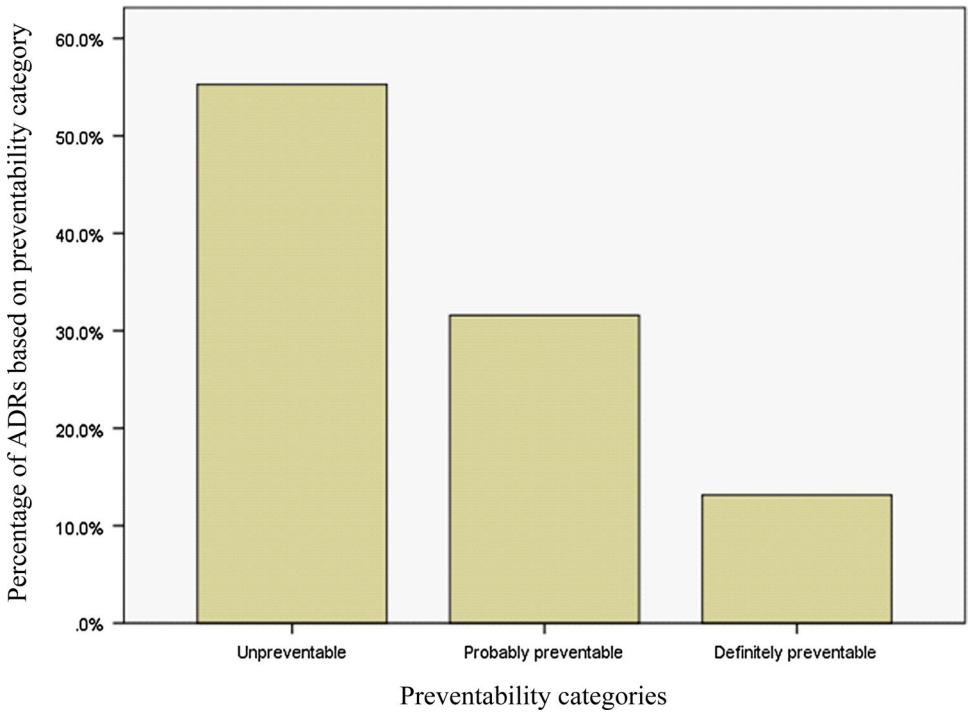

Fig. 2 Percentage for each of the adverse drug reactions (ADRs) preventability category defined using Modified Schumock and Thornton Scale

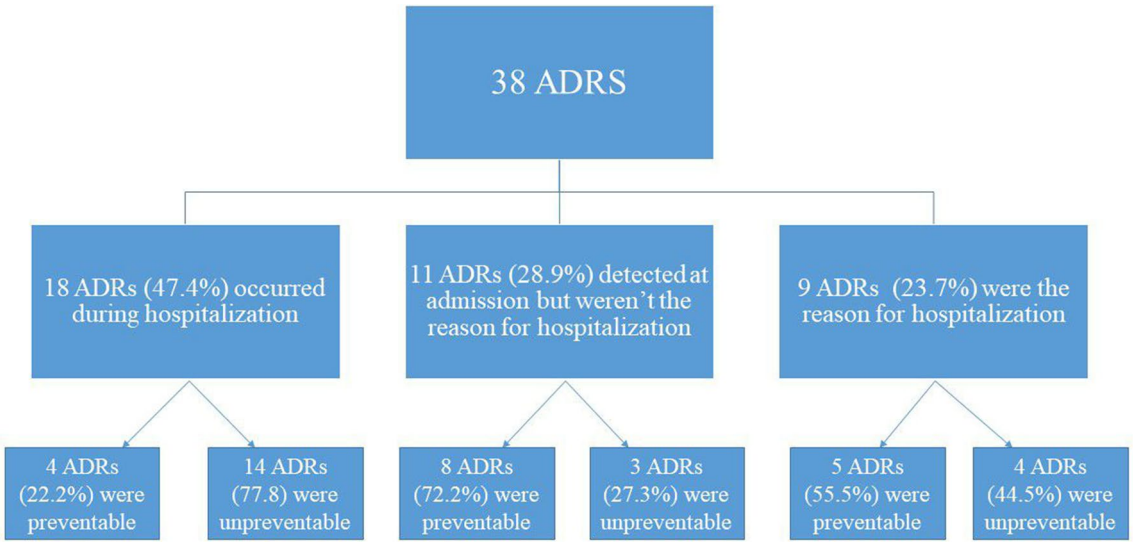

Fig. 3 Preventability of ADRs that occurred during hospitalization, ADRs present upon admission and ADRs related to hospital admission

Factors involved in ADRs preventability

Insufficient monitoring was involved in 5 of the preventable ADRs (29.4%). This was the most prevalent factor. Inappropriate dosing and drug–drug interactions were each independently responsible for 3 (17.6%) of the preventable ADRs, and were considered the second most prevalent factors involved. Poor compliance was the third factor which contributed to 2 (11.8%) of the preventable ADRs. Other involved factors are shown in Fig. 4.

Among the ADRs which occurred during hospitalization, inappropriate dosing was the most common factor responsible for the preventable ADRs, accounting for 2 (50%) of the factors involved in preventability. Drug-drug interactions and taking no preventive measures each independently contributed to 1 patient (25%) of the preventable ADRs. Regarding the preventable ADRs that were presented at admission but were not the cause for hospitalization, insufficient monitoring was the most common factor to preventability (3 patients; 37.5%). Drug-drug interaction was the second factor with 2 ADRs (25%). Finally, for the ADRs that were the cause of admission, insufficient monitoring of the ADRs was the most common factor involved in preventability (40%). Other factors were contraindications, poor compliance and drug–drug interactions, each contributing to 20% of the preventable ADRs. More details of the most common causes and factors that have led to specific ADRs are described in Table 5.

Discussion

Our study has found that about 3% of the hospital admissions were related to ADRs, which is in agreement with a similar study conducted in France showing that 3% of the admissions were related to ADRs [23]. Other studies have reported hospitalization rate resulted from medication related problems (MRPs) in which ADRs have been considered a main contributory factor. In a study which determined the prevalence of hospital admission resulting from MRPs in adult patients with cardiovascular diseases and diabetes in United Kingdom (UK) and Saudi Arabia (SA), 58.7% and 41.5% of MRPs resulted in hospital admissions in the UK and SA, respectively. ADRs were responsible for 45.2% and 20.4% of the MRPs in the UK and SA study, respectively [24].

Preventability of ADRs was a promising finding reported in this study whereby 45% of the ADRs were

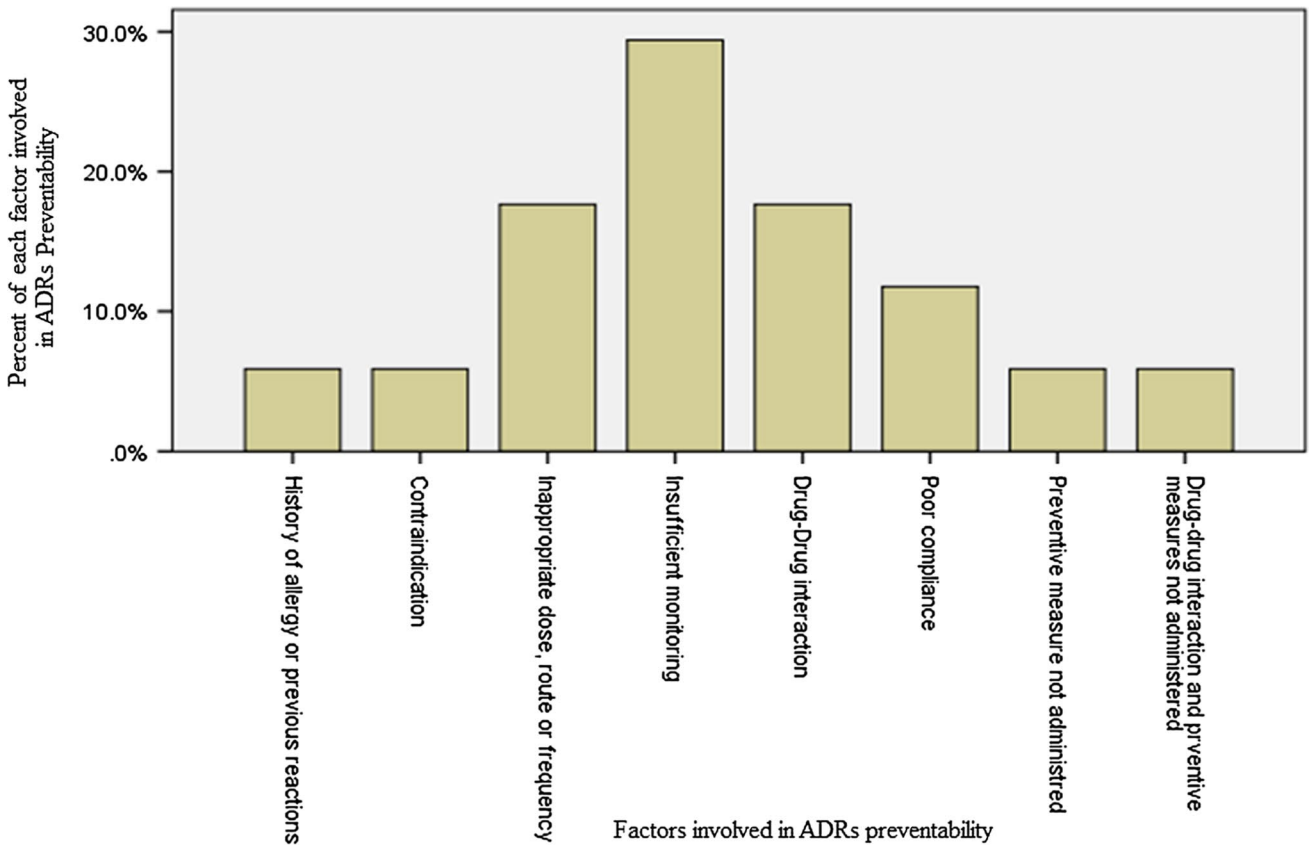

Fig. 4 Percentage of each factor involved in ADRs preventability

Table 5 Examples of most frequent causes/factors involved in the adverse drug reactions (ADRs) preventability identified in the study

ADRs category	Cause/factor	ADRs
ADRs detected upon hospital admission	Insufficient monitoring of electrolytes for patients with chronic use of diuretics	Electrolyte disturbances, such as hypokalemia, hyperkalemia and hyponatermia
	Insufficient monitoring of white blood cells count in patients with chronic use of azathioprine	Neutropenia
	Insufficient monitoring of white blood cells count in patients with chronic use of prednisone	Neutrophilia
	Drug-drug interaction of fluconazole and warfarin	Prolonged prothrombin time
	Drug-drug interaction of ciprofloxacin and warfarin	Prolonged prothrombin time
	Poor patient compliance leading to longer than recommended use of clopidogrel	Ecchymosis
ADRs that were the reason for admission	Insufficient monitoring of potassium in patients receiving torsemide	Symptomatic hypokalemia
	Insufficient monitoring of sodium in patients receiving hydrochlorothiazide	Symptomatic hyponatermia
	Lack of use of a prophylactic medication in elderly patients receiving high doses of both aspirin and prednisone	Gastric ulcer
	Poor compliance in patients receiving high warfarin doses (7.5 mg) versus doctor's recommended dose of 5 mg	Hematoma
ADRs that occurred during hospitalization	Inappropriate dosing (1200 mg) of quetiapine exceeding the maximum allowed daily dose (800 mg)	Acute rise in aspartate transaminase (AST) and alanine transaminase (ALT)
	Inappropriate increase in the dose of spironolactone in a patient with potassium level exceeding 5 meq/L	Hyperkalamia
	Inappropriate increase in the dose of candesartan in a patient with low-normal range blood pressure	Hypotension
	Lack of sufficient use of intravenous hydration or oral hydration in elderly patients before an intravenous contrast media was administered	Acute kidney injury
	Drug-drug interaction of apixaban and clopidogrel	Hematuria

found to be preventable. This finding was in agreement with the result of a Jordanian pilot study which indicated that 50% of the ADRs were preventable [15], and also comparable with the results of studies conducted in Saudi Arabia. One study has been conducted in four hospitals and the other in a 900-bed tertiary academic hospital. They showed that 34.7% and 30% of ADRs were deemed preventable respectively [25, 26]. Our finding was also in agreement with a study conducted in India showing that 55% of the identified ADRs were preventable and the results of a Romanian study, which showed that 41% of the ADRs were preventable [17, 27]. However, the data from two studies carried out in United States and Netherland showed lower preventability for ADRs (28% and 12% respectively) compared with our study finding [28, 29]. This could be explained by the differences in the health care systems imposed by different countries.

The preventability factor analysis in this study indicated that insufficient monitoring, drug–drug interaction and inappropriate dosing were the more frequent factors involved. Such results agreed with the Romanian study which showed that drug–drug interaction, inappropriate dosing and inappropriate monitoring were the most common reasons that deemed an ADRs preventable [27]. In addition, in a literature review of ADRs in hospitalized patients, inappropriate dosing and drug–drug interactions were found to be the most common factors involved in ADRs preventability [30].

ADRs detected upon hospital admission were associated with the highest preventability, followed by ADRs that were the cause of admission, followed by ADRs which occurred during hospitalization which showed the lowest preventability. This could be due to the close monitoring of heath care professionals including clinical pharmacists for patients during hospitalization. Moreover, ADRs detected upon

admission where the reason for admission showed the highest preventability due to the fact that patients fail to communicate with their physicians and/or the physicians did not follow up their patients for routine checkups of ADRs monitoring.

This study has highlighted the national problem of insufficient monitoring as main the factor involved in ADRs preventability and it indicates the importance of adopting strategies to enhance patients follow up and monitoring. Strategies needed to be followed to improve patient's monitoring of ADRs include; increasing physician's awareness of the importance of rescheduling appointments for ADRs monitoring, and increasing pharmacists awareness towards the importance of medicines safety evaluation through counseling about drugs common side effects and encouraging patients' about the importance of reporting suspected ADRs to their healthcare professionals. National campaigns aiming at highlighting the importance of continuous monitoring and reporting of ADRs, and utilizing the available technologies, such as the use of SMS services could be adopted. For ADRs that occurred during hospitalization, inappropriate dosing and drug–drug interaction were the most common factors in their preventability. Utilization of computerized checkup systems upon prescribing patient medications provide a reminder or warning signs for physicians and pharmacists regarding major drug–drug interaction, exceeding maximum doses and the recommended known preventive measures for many ADRs.

Strengths of this study may be the fact that it is the largest investigative research regarding the preventability of ADRs in Jordan. It has reported on factors involved in the preventability of each distinguished category of hospital related ADRs including ADRs detected upon hospital admission, ADRs that caused hospitalization and ADRs which occurred during hospitalization. Study limitations include the involvement of one hospital in Jordan, utilizing medical and surgical wards only which may have affected the results as a whole. Lack of involvement of intensive care departments in the study could have led to a lower number of identified ADRs.

Conclusion

Conducting the current observational prospective study on ADRs preventability analysis in the hospital setting unveiled important factors and problematic medications involved in causing the identified ADRs. In this study in Jordan, almost half of the ADRs identified were found to be preventable. Insufficient patient monitoring was the main factor involved in the preventability of admissions caused by ADRs. It was also the most frequent factor involved in the preventability of ADRs detected upon hospitalization. With such information, insights into the most preventative strategies that can be followed by healthcare professional are provided. Future studies can be extended to include more hospitals, ICU and CCU units and the emergency department. Also, studies aimed at assessing the benefits of implementing strategies targeting ADRs preventability would be definitely required.

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Data Availability The datasets generated during and/or analysed during the current study are available fromthe corresponding author on reasonable request.

Conflicts of interest The authors declare no conflict of interests.

Appendix 1: Data retrieved from the patients' medical records for study assessments

Demographics questionnaire: Patients' demographics, medications and current medical conditions.
Patient age:

Patient gender:

Date of admission:

Ward of admission:

Cause of admission:

Presence of ADRs upon admission: yes no

Current diseases and medical conditions:

Past medications (including doses and frequencies):

Currently prescribed medications (including doses and frequencies)

Appendix 2: An evaluation form used for data collection regarding the systems affected by the adverse drug reaction (ADRs)

Date of suspected ADRs detection:

Gastrointestinal: Abdominal pain/vomiting/nausea/gastritis/gastric or peptic ulcer/GI bleeding

Renal: acute renal failure, acute interstitial nephritis

Metabolic: hypokalemia, hyperkalemia, hyponatremia, hypocalcemia, hypercalcemia, hypomagenismia, hypermagensimia, hyperuricemia

Vascular: Hematoma, hemorrhage

Hepatic: Increased liver enzyme, hepatitis, cholestasis

Cardiac: Bradycardia, Tachycardia (palpitations), QT prolongation, IV block, hypotension

Respiratory: Cough, shortness of breath, bronchospasm

Dermatological: Rash, angioedema, urticaria, erythma, Steven's Johnson's syndrome. Toxic epidermal necrolysis, exanthema

Urological: Urinary retention, urinary incontinence

Others:

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