Incidence of Adverse Drug Reactions in Two Tertiary Hospitals: A Prospective Observational Study

Malahat Khalili

Guilan University of Medical Sciences <https://orcid.org/0000-0001-6160-0913>

Hamid Sharifi

Kerman University of Medical Sciences

Bita Mesgarpour

National Institute for Medical Research Mwanza Research Centre

Fatemeh Dabaghzadeh

Kerman University of Medical Sciences Faculty of Pharmacy

Ali Akbar Haghdooost (✉ ahaghdooost@gmail.com)

Kerman University of Medical Sciences

Research Article

Keywords: Incidence, adverse drug reactions, tertiary hospitals, prospective observational study, healthcare delivery quality, mortality, economic burden, constant intensive monitoring

Posted Date: August 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-818170/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Monitoring and detecting adverse drug reactions (ADRs) in hospitals is crucial to improving drug safety and healthcare delivery quality. Nevertheless, there was not enough information on ADR incidence and its figure in Iran.

Aim: this study aimed to determine the incidence of ADRs in hospitalized patients and investigate their characteristics in Iran.

Methods: We conducted a three-month prospective study in two tertiary hospitals in 2019. All admitted patients were intensively monitored for all suspected ADRs through daily visiting hospital wards and soliciting information from physicians, nurses and interviewing suspicious patients. We calculated the incidence of ADRs, and 95% confidence intervals (95% CI). Poisson regression was used to evaluate risk factors for ADR incidence.

Results: Among 13,613 admitted patients, we detected 115 ADRs in 114 patients. The incidence of ADR was 8.4 per 1000 admissions (95% CI: 7.0-10.1), and 13.9% of them were ADR-related hospital admissions. The risk of ADRs was significantly predicted by age, length of hospital stay, patients' diagnostics, number of drug usage, and using respiratory system agents and anti-infectives for systemic use. The most common ADRs were skin and subcutaneous manifestations (52.2%), and 62.6% of ADRs were caused by anti-infectives (commonly vancomycin, ceftriaxone, and ciprofloxacin).

Conclusion: This study indicated that ADRs occurrence during the hospital stay or resulting in hospital admissions are considerable. Given that ADR occurrence could be associated with increased morbidity, mortality, and economic burden, constant intensive monitoring is required to address the drug safety issue and promote actions to improve patient safety and reduce the health and economic burden.

Impacts On Practice

- Early detection of adverse drug reactions (ADRs) is crucial, particularly in hospitals, where systems for detecting ADRs can save lives and money.
- We observed that the occurrence of ADRs was prevalent in both studied hospitals. Then Intensive monitoring can be a valuable tool in the early detection, management, and treatment of ADRs.
- Understanding the epidemiology and risk factors of ADRs is crucial for policy-makers to develop appropriate prevention strategies.

Aim Of The Study

Therefore, this study aimed to determine the incidence of ADRs in hospitalized patients, characterize identified ADRs and implicated medication, and identify factors that increase the risk of ADRs in two tertiary university hospitals in Iran.

Introduction

An adverse drug reaction (ADR) is an undesirable effect, reasonably associated with the use of the drug that may occur as part of a drug's pharmacological action or may be unpredictable in its occurrence [1]. They cause significant morbidity and mortality and represent a substantial burden on health care resources. ADRs are responsible for 4.9% to 8.7% of hospital admissions [2], and it was varied from 0.5% to 12.8% in Europe [3]. Moreover, it may occur in 1.6% to 41.4% of patients during hospital stay [3-5]. Previous studies showed that about 11% to 31% of ADRs were serious or severe, 1.4% to 12% life-threatening, 1% to 2% lethal [6-8]. According to a systematic review in 2013, the overall cost for a hospitalized patient with an ADR was reported to be \$2,401 per patient [9].

Improving patient safety is now a government priority in many countries [10]. Early detection is essential, particularly in hospitals, where systems for detecting ADRs can save lives and money. Lessons learned from ADR detection may help prevent some future reactions [11]. So monitoring and documentation of ADRs are crucial to ensure the safe use of medications [12]. By contrast, data on ADRs occurring after hospital admissions are inconsistently documented [13]. Spontaneous, voluntary reporting schemes involving medical staff provide only limited information due to deficient reporting of ADRs around the world [14]. Though, intensive monitoring could give the most reliable figures on the incidence and the pattern of ADRs and thereby helps to design improvement strategies for drug safety and safe use [15]. However, continuous intensive monitoring programmes are costly and time-consuming [16,17].

In Iran, a study in an internal medicine ward showed that 11.8% of admitted patients (47 ADR in 400 patients) experienced at least one ADR [18]. In another study, ADR incidence was 1.6% in admitted patients (112 in 6840 patients), and 58.2% of reported reactions were due to anti-infective agents such as ceftriaxone. Moreover, the skin and the appendages system was the most frequently affected system [19]. In a referral hospital in Tehran, 43.1% of reported reactions were due to anti-infective agents, and 21.9% of all reactions affected the gastrointestinal system [20]. A study by Shalviri et al. also showed that 5.8% (1205 of 20,877 reports) reported ADRs to Iranian pharmacovigilance center were related to ceftriaxone from 1998 through 2009. Ceftriaxone with 49 death was also responsible for the highest number of ADR-related deaths [21]. In another study during 2004-2018, 2310 of 4425 (52.2%) ADRs reports received by the regional pharmacovigilance center were caused by anti-infective agents, and most of the ADRs had skin and hair manifestations (50.6%) [22]. However, there is a lack of updated information about the most common ADRs and most frequently drugs responsible for ADR occurrence in Iran.

Iran Food and Drug Administration established a national pharmacovigilance center in 1997 to receive spontaneous reports from healthcare professionals. Though, there is a considerable underreporting of ADRs to this spontaneous reporting systems [23]. The leading cause of underreporting in Iran is unawareness of the existence of a national pharmacovigilance center [24,25], poor knowledge regarding reporting [26,27], and fear of punishment and criticism [26]. Thus, implementing active ADR detection and

reporting in hospitals could be a constructive action in improving the awareness of unintended effects of medicines and patient safety and strengthening the national pharmacovigilance systems.

Methods

A detailed description of study methodology has been previously reported [23,28]. The following provides a summary with relevant additional detail as needed.

Study design and setting

A three-month prospective observational study was carried out in two tertiary university hospitals in Iran in 2019. **Table 1** summarizes the overall characteristics of Afzalipour (A) hospital in Kerman city, southeast, and Razi (R) hospital in Rasht city, north of Iran. All admitted patients (inpatients and outpatients) of each sex and any age that used prescribed medication in our study wards were included in the study and traced for the occurrence of ADR. Moreover, all patients who developed a suspected ADR after admission or who were admitted primarily to treat an ADR during the study period were considered ADR patients. The exclusion criteria were considered as patients who developed an ADR due to intentional or accidental poisoning, ADRs due to the fresh blood/blood products, drug overdose, and patients with drug abuse and intoxication.

Data Collection

A trained epidemiologist (MK) actively identified all suspected ADR through daily visiting hospital wards and soliciting information from physicians, nurses, and interviewing suspicious patients. ADRs were defined according to the definition of WHO: “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” [29]. All identified suspected ADR cases were reviewed and confirmed by a clinical pharmacist.

Data were recorded using a structured ADR reporting form. For the suspected ADR patients, data about age, gender, hospital medical wards, diagnosis, reactions, prescribed drugs, drugs causing ADRs, and length of hospital stay were collected through interviews with the patients and reviewing their medical records. For all the non-ADR patients, data about age, gender, diagnosis, prescribed drugs, and length of hospital stay were retrieved from the Hospital Information System (HIS) database.

We used Anatomical Therapeutic Chemical (ATC) classification system^[30] and upper-level categories of Medical Dictionary for Regulatory Activities Terminology (MedDRA)^[31] to classify the medications, diagnosis and clinical manifestations of patients, respectively.

Statistical analysis

We calculated the ADR incidence per 1000 admissions with 95% confidence intervals (95% CI) for each hospital in the study period according to the detected ADRs. The bivariate Poisson regression analysis

was used to determine the association between ADR incidence and age, gender, studied hospitals (A and R), length of hospital stay, category of the diagnosis, prescribed drug classes, and the number of prescribed drugs. A cut-off point for poly-pharmacy was ≥ 6 medications [32,33].

Having reviewed the frequency of ADR in each medical diagnosis, we created three groups of diagnoses according to quartile cut-points for the relative frequency of ADR as presented in **Supplementary Table 1**. Diagnoses with an ADR relative frequency of 0.87% and lower (first quartile) were classified as low-risk, including blood and lymphatic system disorders, congenital, familial, and genetic disorders, immune system disorders, ear and labyrinth disorders, endocrine disorders, hepatobiliary disorders, infections and infestations, investigations, musculoskeletal and connective tissue disorders, neoplasms benign, malignant and unspecified, nervous system disorders, renal and urinary disorders, psychiatric disorders, reproductive system and breast disorders, skin and subcutaneous tissue disorders, surgical and medical procedures, and vascular disorders. Diagnoses which their ADR relative frequency was between 0.88% and 5.48% (second and third quartile) were categorized as medium-risk diagnoses such as cardiac disorders, injury, poisoning and procedural complications, metabolism and nutrition disorders, and pregnancy, puerperium and perinatal conditions. At last, diagnoses with an ADR relative frequency of 5.49% and higher (fourth quartile) were considered as high-risk diagnoses that included gastrointestinal disorders, general disorders and administration site conditions, respiratory, thoracic and mediastinal disorders.

Then, multivariable Poisson regression models were applied to determine the factors associated with ADR incidence. Variables with a P-value less than 0.2 in the bivariate analysis were entered into the multivariable Poisson model. Incidence Rate Ratios (IRRs) and 95% CIs were estimated according to this model. Statistical analyses were performed using Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, USA) and STATA version 16.0 (StataCorp., College Station, TX, USA). A P-value < 0.05 was considered statistically significant.

Results

During the study period, a total of 13,613 patients were admitted at R and A hospitals. Of them, 6,299 patients were male (46.3%), and the average age of patients was 41.5 ± 25.2 years (ranged from one day to 121 years). We detected 115 ADR in 114 patients, and the incidence of ADR was 8.4 per 1000 admissions (95% CI: 7.0-10.1). The ADR incidence was 7.9 ($n = 69$, 95% CI: 6.1-10.0) and 9.4 ($n = 46$, 95% CI: 6.9-12.5) in Hospitals A and R, respectively with no significant difference between two hospitals (P-value = 0.174). Moreover, 16 of these patients (13.9%) admitted to these hospitals with ADR. The majority of ADRs detected in pediatrics, including 13.9% ($n = 16$) in pediatric wards (internal and surgical), 2.6% in neonatal intensive care unit (NICU) ($n = 3$), 1.7% in pediatric intensive care unit (PICU) ($n = 2$), and 1.7% in the pediatric emergency ($n = 2$). Among adult wards, most ADRs were seen in surgical ($n = 13$, 11.3%) and emergency ($n = 11$, 9.6%) wards. Women experienced more ADRs ($n = 67$, 58.8%) than men ($n = 47$, 41.2%) but this difference was not significant (P-value = 0.280). Furthermore, the mean age of patients with ADRs was 39.5 (se = 2.2) years. According to the bivariate regression analysis, there is no statistically

significant relationship between age groups and the risk of ADR. However, in the multivariable analysis, the risk of ADR in the age group over 60 years was 60% lower than under 15 years old group (P-value= 0.007) (**Table 2**).

The length of hospital stay for patients with ADRs was significantly longer (interquartile range (IQR) = 9.8) compared with those who did not experience ADRs (IQR=4) ($Z = 5.52$, $P < 0.001$). ADR incidence also increased by almost 4% (IRR=1.04) with each additional day's stay in the hospital. In high-risk and moderate-risk diagnoses, the risk of ADR occurrence was increased significantly by about 3.5 times compared to low-risk diagnoses. The patients with ADR took about eight drugs on average during hospital stay. The multivariate regression results showed that in patients who received six or more drugs, the risk of ADR incidence was 2.34 times higher than patients who took fewer drugs (P-Value = 0.009). (**Table 3**)

Anti-infectives were prescribed for 86% of patients with ADR (98 cases), and the risk of developing ADR in these patients was 3.3 times higher than in patients who did not take this drug class (P-value<0.001). The effect of subsets of this class of drugs on the risk of ADR was also investigated. The results showed that patients receiving beta-lactam antibacterial (penicillins and other beta-lactams) (IRR = 1.7, 95% CI: 1.2-2.5), quinolone antibacterials (IRR = 1.9, 95% CI: 1.4-2.8), other antibacterials (IRR = 1.7, 95% CI: 1.1-2.5), macrolides, lincosamides and streptogramins (IRR = 1.6, 95% CI: 1.1-2.6) and immune serum and immunoglobulins (IRR = 9.3, 95% CI: 3.9-22.0) had a significantly higher risk of ADR incidence. The ADR risk was also increased by about two times (P-value=0.003) in patients taking respiratory system agents. In this category, drugs for obstructive airway diseases (IRR=2.0, 95% CI: 1.3-3.0) and antihistamines (IRR=4.5, 95% CI: 3.0-7.0) considerably increased the risk of ADR occurrence in patients.

The most commonly identified ADRs were skin itch (28.7%), urticaria (16.5%), rash (13.9%), fever (13.9%) and respiratory distress (9.6%). **Fig. 1** shows body systems most commonly affected by an ADR. Moreover, we detected some severe reactions such as tachycardia in five patients (4.3%), Steven-Johnson syndrome in four patients (3.5%), Acute Generalized Exanthematous Pustulosis (AGEP) in one patient, generalized blistering in one patient, anaphylactic shock in one patient, and generalized edema in one patient. A total of 4.3% of severe ADR patients (n=5) were required to transfer to a higher level of care, such as ICU. The details of identified ADR are presented in **Supplementary Table 2**.

As Fig. 2 shows, the drug class most commonly implicate with ADRs was anti-infectives (62.6%), so 19.1%, 11.3%, and 8.7% of ADRs were due to vancomycin ceftriaxone, and ciprofloxacin respectively. Nervous system agents (7.8%) and blood and blood forming organs (6.1%) were other prevalent offending classes of drugs. The details of drugs associated with ADR are shown in Supplementary Table 3.

Discussion

This study showed that the incidence of ADR was 8.4 per 1000 admissions, and 13.9% of them were ADR-related hospital admissions. According to the Poisson regression model, age, length of hospital stay,

type of medical diagnosis, number of prescribed drugs, use of anti-infectives for systemic use, and respiratory system agents were significantly associated with ADR incidence. Moreover, nearly half of all reactions lead to skin and subcutaneous tissue disorders. Anti-infectives were also the most common class of drugs related to ADRs occurrence.

This prospective study showed that ADR's occurrence is prevalent in hospitalized patients of two studied hospitals, and 16 patients (out of 115 patients with ADRs) required hospitalization to manage the conditions. Other previous studies in Iran reported a higher proportion of ADRs so that this incidence was between 16.4 and 117.5 per 1000 admissions [18,19,34] in Tehran's university hospitals. Moreover, a systematic review showed the median of ADRs occurrence during hospitalization was 101 per 1000 patients in Europe [3]. A meta-analysis study estimated ADRs might occur in 169 per 1000 patients during hospitalization [5], and in another systematic review, it ranged from 17 to 518% per 1000 admissions [4]. Angamo et al. indicated that the median of ADR-related hospitalization in developed and developing countries was 63 and 55 per 1000 admissions, respectively [35]. However, our figure was considerably lower than this systematic review estimate. The possible explanations for these variations may be differences in ADRs recognition and documentation, the definition of ADR, studied populations, and settings in which the studies were performed.

Hospitalized patients are exposed to multiple risk factors predisposing them to ADRs, and patients' diagnosis has been reported as significant risk factors for developing ADRs [36]. The current study showed that patients with diagnoses such as gastrointestinal disorders, general disorders and administration site conditions, respiratory disorders, cardiac disorders, poisoning and procedural complications, metabolism disorders, pregnancy and perinatal conditions were at a higher risk of ADR. According to MedDRA categories, patients admitted to hospitals with ADR were categorized to general disorders and administration site conditions, leading to a higher risk of this diagnosis than other diagnoses. On the other hand, patients in these diagnostic categories may be more at risk, like pregnant women in the diagnostic category of pregnancy, puerperium and perinatal conditions, and the age and number of prescribed drugs in these patients might be different compared to patients with other diagnoses. These patients may have altered pharmacodynamic and pharmacokinetic mechanisms due to drug-disease interaction predisposing them to ADRs [37]. However, more research would be required to identify the effect of diagnosis on ADR occurrence.

Furthermore, there was a significant association between the length of hospital stay and ADR incidence; the average length of hospital stay was more than two-fold in patients who experienced ADRs, compared to patients without ADRs. Previous studies found that the duration of hospital stay was prolonged in patients with ADRs; ranged from 1.9 to 9.3 days [38-43]. A systematic review clarified that hospitalization length is the proxy measure of comorbidity and chronic illness with an increased number of prescribed drugs at higher doses, reflecting an increased risk of ADR [37]. While the occurrence of an ADR could contribute to raised hospital stays. Further studies are needed to determine the direction of a causal relationship between the length of hospital stay and ADR incidence.

Most ADRs occurred in children and patients aged 60 or over in this study. Nevertheless, the risk of ADR incidence was significantly lower in the patients aged 60 or older than in those below 15 years. Pediatric populations are especially vulnerable to ADRs [44,45] due to the lack of safety data for this age group from the drug development process, the wide use of off-label, and the level of maturity of body systems [46]. However, a meta-analysis estimated that about one in ten hospital admissions of older patients is due to ADRs [47]. According to the findings of previous studies, the incidence of ADRs is prevalent in elderly patients due to increased age, deteriorating organ function, reduced hepatic and renal function, poly-morbidity, poly-pharmacy, usage of over-the-counter drugs, and alternative medicine [37,48,49].

Our study showed that the utilization of a large number of medications is a risk factor for ADR incidence. The ADR incidence had significantly increased more than two times with increasing the number of drugs from 1-5 drugs to six drugs and above. In the previous studies, ADR incidence had a statistically significant relationship with the number of drugs used [32,50,51]. Both comorbidities and the number of medications contribute to complexities in patients' condition and are associated with an increased risk for ADR [32]. Efforts to reduce poly-pharmacy are essential, but the number of medications cannot always be reduced without harming many patients. Then it is crucial to understand the basis for drug interactions. This knowledge will allow physicians to make the most appropriate choices in prescribing and avoiding preventable ADRs [52].

Multivariable regression had shown that prescription of respiratory system agents had increased the risk of ADR nearly two times, and patients taking drugs for obstructive airway diseases and antihistamines for systemic use were significantly at risk of developing ADR. In some previous studies, respiratory system agents had not considerable effect on ADR incidence [53,54]. However, Fauzi Dali et al. reported that respiratory system agents such as drugs for obstructive airway diseases are common therapeutic groups causing ADR [55]. Antihistamines have several adverse effects related to their antihistaminic actions [56]; as well as, Tjalling e al. showed that antihistamines are frequently associated with ADRs such as skin eruptions and headache [57]. Given the widespread consumption of antihistamines, it is important to consider appropriateness of their prescriptions and monitoring of their probable adverse effects

Furthermore, anti-infectives for systemic use, almost most of its subcategories, significantly increased ADR occurrence in patients. Broad-spectrum antibiotics are generally well-tolerated antibiotics; however, adverse effects have been reported that are likely due to an increased prescription of these drugs as first-line therapy [58,59]. Cross-reactivity between anti-infectives is challenging to predict due to the small number of patients with ADR. Moreover, anti-infective was the most common drug class that directly caused ADRs, and the most common anti-infective associated with ADRs was vancomycin and ceftriaxone. This pattern is similar to the Iranian pharmacovigilance center's figure from 1998 to 2009 [21], and previous studies carried out in Iran [19,22,34,60] and other countries [61,62]. While cardiovascular agents [63,64], insulin [43], nonsteroidal anti-inflammatory drugs [43,47], and diuretics [65,66] were the most common class of drugs that cause ADRs in other studies. This difference

is probably due to the higher rate of antibiotics prescribed and misused in Iran [60,67] since Hatam et al. showed that in 98% of all surgical procedures, antibiotics were misused [68]. Self-medication and the irrational use of antibiotics are also common among Iranian communities [69]; while, more attention is often paid to prescription and consuming other drug classes.

The most common ADRs affected the skin and subcutaneous tissue (such as itch, erythema, and rash) in our study, consistent with the figure of previous studies in Iran [19,70] and Italy [62]. Although, in other studies, the gastrointestinal system [13,20,34,63] and central nervous system [43] were the most frequently affected systems. In fact, the body systems mainly affected followed the pattern of medications causing ADRs [43]. Chan et al. suggested that at least part of these ADRs could be predicted or avoided using pharmacogenomic testing [63]. In this study, ADRs were detected according to observable clinical manifestation by nurses and physicians. The pathological and laboratory data, which are objective markers of ADRs, should be considered for ADR detection.

There are a few limitations of this study that merit consideration. Firstly, the diagnosis of a potential ADR was dependent on clinical judgment. Patients, especially who are stayed in ICU wards, often had underlying conditions that may contribute to their presenting complaint or status, and the role of the suspected drug(s) can be difficult or impossible to determine. Secondly, we evaluated the effect of limited risk factors for ADR incidence; we suggest future research to assess the impact of other essential factors such as comorbidities and history of ADRs and allergy. Thirdly, this study was conducted in two hospitals, and the variation between different hospitals is likely because of differences in the local population characteristics and the specialties within the hospitals. However, we selected two hospitals in two cities (one in the north and one in the southeast of the country) with diverse wards that were representative of the clinical specialties.

Intensive monitoring in detecting ADR can help to improve the quantity and quality of reporting to pharmacovigilance centers. We suggested further improve drug safety by raising the physicians' and nurses' awareness about ADR, ADR detecting, and reporting. Moreover, pharmacists and clinical pharmacists could have an important role. When designing policies that intend to reduce the burden of ADRs, it is essential to know which ADRs and which medicines are causing the majority of ADRs in the country. Furthermore, pharmacotherapy still needs evidence-based strategies to improve patients' care, including education, monitoring, planning for medications after ADR occurrence, and implementing prophylactic measures when applicable. It is also crucial for guiding health policy concerning medicine prescription, particularly antibiotic usage. Therefore, more epidemiological studies have been suggested on ADR occurrence.

Conclusion

This study indicates that ADR incidence during the hospital stay or resulting in hospital admission is considerable. Patients under 15 years of age, prolonged length of hospital stay, poly-pharmacy, patients' diagnostics, and using respiratory system agents and anti-infectives for systemic use were significantly

associated with a higher risk of ADRs occurrence. Anti-infectives were the most common causative agent for ADRs, and skin manifestations were the most frequently experienced symptom. ADR occurrence could be associated with increased morbidity, mortality, and economic burden; then, steps should be taken to introduce strategies to reduce their impact. The results of this study may further promote actions to improve patients' safety.

Declarations

Acknowledgments: The authors would like to especially thank and appreciate all staff of Afzalipour and Razi hospitals for their comprehensives support for this study.

Funding: This study was supported by Kerman University of Medical Sciences, Kerman, Iran.

Conflicts of interest/Competing interests: The authors declare no competing interests.

Data availability statement: The data that support the findings of this study are available from the lead author [M,Kh] upon reasonable request.

Ethical approval

The study protocol was assessed and approved by the Research Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (IR.KMU.REC.1397.543). Following the discussions about the study's purpose and ensuring secured confidentiality, we obtained verbal consent from all participants. To maintain confidentiality, names were not identified on the notes, and they were assigned a unique code.

References

1. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *The lancet*. 2000;356(9237):1255-1259.
2. Oscanoa T, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *European journal of clinical pharmacology*. 2017;73(6):759-770.
3. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. *Drug Safety*. 2015 2015/05/01;38(5):437-453.
4. Cano FG, Rozenfeld S. Adverse drug events in hospitals: a systematic review. *Cadernos de Saúde Pública*. 2009;25:S360-S372.
5. Miguel A, Azevedo LF, Araújo M, et al. Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis. *Pharmacoepidemiology and drug safety*. 2012;21(11):1139-1154.
6. Boeker EB, de Boer M, Kiewiet JJS, et al. Occurrence and preventability of adverse drug events in surgical patients: a systematic review of literature. *BMC Health Services Research*. 2013

7. Alshehri GH, Keers RN, Ashcroft DM. Frequency and nature of medication errors and adverse drug events in mental health hospitals: a systematic review. *Drug Safety*. 2017;40(10):871-886.
8. Tandon VR, Khajuria V, Mahajan A, et al. Fatal adverse drug reactions: Experience of adverse drug reactions in a tertiary care teaching hospital of North India - A case series. *Indian journal of critical care medicine*. 2014;18(5):315-319.
9. Khan LM. Comparative epidemiology of hospital-acquired adverse drug reactions in adults and children and their impact on cost and hospital stay—a systematic review. *European journal of clinical pharmacology*. 2013;69(12):1985-1996.
10. U.S. Department of Health and Human Services OoDPaHP. National action plan for adverse drug event prevention. Washington, DC: U.S. Department of Health & Human Services 2014. p. 50-98.
11. Benkirane RR, Redouane R, Haimeur CC, et al. Incidence of adverse drug events and medication errors in intensive care units: a prospective multicenter study. *Journal of patient safety*. 2009;5(1):16-22.
12. Clavenna A, Bonati M. Adverse drug reactions in childhood: a review of prospective studies and safety alerts. *Archives of disease in childhood*. 2009;94(9):724-728.
13. Davies EC, Green CF, Taylor S, et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS One*. 2009;4(2):e4439-e4439.
14. Li R, Curtain C, Bereznicki L, et al. Community pharmacists' knowledge and perspectives of reporting adverse drug reactions in Australia: a cross-sectional survey. *International Journal of Clinical Pharmacy*. 2018 2018/08/01;40(4):878-889.
15. He W, Yao D, Hu Y, et al. Analysis of a pharmacist-led adverse drug event management model for pharmacovigilance in an academic medical center hospital in China. *Ther Clin Risk Manag*. 2018;14:2139-2147.
16. Masino AJ, Forsyth D, Fiks AG. Detecting adverse drug reactions on Twitter with convolutional neural networks and word embedding features. *Journal of Healthcare Informatics Research*. 2018;2(1-2):25-43.
17. Thuermann PA, Windecker R, Steffen J, et al. Detection of adverse drug reactions in a neurological department. *Drug safety*. 2002;25(10):713-724.
18. Pourseyed S, Fattahi F, Pourpak Z, et al. Adverse drug reactions in patients in an Iranian department of internal medicine. *Pharmacoepidemiology and Drug Safety*. 2009;18(2):104-110.
19. Baniasadi S, Fahimi F, Shalviri G. Developing an Adverse Drug Reaction Reporting System at a Teaching Hospital. *Basic & Clinical Pharmacology & Toxicology*. 2008;102(4):408-411.

20. Baniasadi S, Fahimi F. Adverse Drug Reactions in a Pulmonary Teaching Hospital: Incidence, Pattern, Seriousness, and Preventability. *Current Drug Safety*. 2011 //;6(4):230-236.
21. Shalviri G, Yousefian S, Gholami K. Adverse events induced by ceftriaxone: a 10-year review of reported cases to Iranian Pharmacovigilance Centre. *Journal of Clinical Pharmacy and Therapeutics*. 2012;37(4):448-451.
22. Izadpanah F, Amini M, Asadollahpour A, et al. Adverse Drug Reactions in Mazandaran Province, Iran, 2004-2018. *Journal of Mazandaran University of Medical Sciences*. 2020;30(185):96-103.
23. Khalili M, Mesgarpour B, Sharifi H, et al. Estimation of adverse drug reaction reporting in Iran: Correction for underreporting. *Pharmacoepidemiology and Drug Safety*.n/a(n/a).
24. Hanafi S, Torkamandi H, Hayatshahi A, et al. Knowledge, attitudes and practice of nurse regarding adverse drug reaction reporting. *Iran J Nurs Midwifery Res*. 2012;17(1):21-25.
25. Isfahani ME, Mousavi S, Rakhshan A, et al. Adverse drug reactions: knowledge, attitude and practice of pharmacy students. *J Pharm Care*. 2013;1(4):145-148.
26. Mirbaha F, Shalviri G, Yazdizadeh B, et al. Perceived barriers to reporting adverse drug events in hospitals: a qualitative study using theoretical domains framework approach. *Implement Sci*. 2015;10:110.
27. Afifi S, Maharloui N, Peymani P, et al. Adverse drug reactions reporting: pharmacists' knowledge, attitude and practice in Shiraz, Iran. *Int J Risk Saf Med*. 2014;26(3):139-145.
28. Khalili M, Sharifi H, Mesgarpour B, et al. Evaluation of Pharmacovigilance System in Iran. *International Journal of Health Policy and Management*. 2020.
29. Edwards IR, Biriell C. Harmonisation in Pharmacovigilance. *Drug safety*. 1994;10(2):93-102.
30. WHO Collaborating Centre for Drug Statistics Methodology. The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) Oslo, Norway: WHO Collaborating Centre; 2020 [cited 2020 November 19]. Available from: <https://www.whocc.no/>
31. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf*. 1999 Feb;20(2):109-17.
32. Angamo MT, Curtain CM, Chalmers L, et al. Predictors of adverse drug reaction-related hospitalisation in Southwest Ethiopia: A prospective cross-sectional study. *PLOS One*. 2017;12(10):e0186631.
33. Bushardt RL, Massey EB, Simpson TW, et al. Polypharmacy: misleading, but manageable. *Clin Interv Aging*. 2008;3(2):383-389.

34. Baniasadi S, Habibi M, Haghgoo R, et al. Increasing the number of adverse drug reactions reporting: the role of clinical pharmacy residents. *Iran J Pharm Res*. 2014 Winter;13(1):291-297.
35. Angamo MT, Chalmers L, Curtain CM, et al. Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries: A Review of Prevalence and Contributing Factors. *Drug Safety*. 2016 2016/09/01;39(9):847-857.
36. Mugoša S, Bukumirić Z, Kovačević A, et al. Adverse drug reactions in hospitalized cardiac patients: characteristics and risk factors. *Vojnosanitetski pregled*. 2015;72(11):975-981.
37. DAHIYA S. A systematic review of risk factors of adverse drug reactions in hospitalized patients. *Asian J Pharm Clin Res*. 2018;11(10):25-29.
38. Poudel DR, Acharya P, Ghimire S, et al. Burden of hospitalizations related to adverse drug events in the USA: a retrospective analysis from large inpatient database. *Pharmacoepidemiol Drug Saf*. 2017;26(6):635-641.
39. Hug BL, Keohane C, Seger DL, et al. The costs of adverse drug events in community hospitals. *Jt Comm J Qual Patient Saf*. 2012;38(3):120-126.
40. Hoogervorst-Schilp J, Langelaan M, Spreeuwenberg P, et al. Excess length of stay and economic consequences of adverse events in Dutch hospital patients. *BMC Health Serv Res*. 2015;15(1):531.
41. Khan LM. Comparative epidemiology of hospital-acquired adverse drug reactions in adults and children and their impact on cost and hospital stay – a systematic review. *Eur J Clin Pharmacol*. 2013;69(12):1985-1996.
42. Rottenkolber D, Schmiedl S, Rottenkolber M, et al. Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. *Pharmacoepidemiol Drug Saf*. 2011;20(6):626-634.
43. Fasipe OJ, Akhideno PE, Owhin OS. The observed effect of adverse drug reactions on the length of hospital stay among medical inpatients in a Nigerian University Teaching Hospital. *Toxicology Research and Application*. 2019 2019/01/01;3:2397847319850451.
44. Kurian J, Mathew J, Sowjanya K, et al. Adverse Drug Reactions in Hospitalized Pediatric Patients: A Prospective Observational Study. *The Indian Journal of Pediatrics*. 2016 2016/05/01;83(5):414-419.
45. Nogueira Guerra L, Herdeiro MT, Ribeiro-Vaz I, et al. Adverse drug reactions in children: a ten-year review of reporting to the Portuguese Pharmacovigilance System. *Expert Opinion on Drug Safety*. 2015 2015/12/02;14(12):1805-1813.
46. Elzagallaai A, Greff M, Rieder M. Adverse Drug Reactions in Children: The Double-Edged Sword of Therapeutics. *Clinical Pharmacology & Therapeutics*. 2017;101(6):725-735.

47. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *European Journal of Clinical Pharmacology*. 2017 2017/06/01;73(6):759-770.
48. Carnovale C, Gentili M, Fortino I, et al. The importance of monitoring adverse drug reactions in elderly patients: the results of a long-term pharmacovigilance programme. *Expert Opinion on Drug Safety*. 2016 2016/02/01;15(2):131-139.
49. Schurig AM, Böhme M, Just KS, et al. Adverse Drug Reactions (ADR) and Emergencies. *Dtsch Arztebl Int*. 2018;115(15):251-258.
50. Rydberg DM, Holm L, Engqvist I, et al. Adverse Drug Reactions in a Tertiary Care Emergency Medicine Ward - Prevalence, Preventability and Reporting. *PLOS One*. 2016;11(9):e0162948.
51. Sugioka M, Tachi T, Mizui T, et al. Effects of the number of drugs used on the prevalence of adverse drug reactions in children. *Scientific Reports*. 2020 2020/12/07;10(1):21341.
52. U.S. Food and Drug Administration. Preventable Adverse Drug Reactions: A Focus on Drug Interactions U.S.: FDA; 2018 [cited 2020 December 30]. Available from: <https://www.fda.gov/drugs/drug-interactions-labeling/preventable-adverse-drug-reactions-focus-drug-interactions>
53. Patidar D, Rajput MS, Nirmal NP, et al. Implementation and evaluation of adverse drug reaction monitoring system in a tertiary care teaching hospital in Mumbai, India. *Interdisciplinary toxicology*. 2013;6(1):41-46.
54. Conforti A, Opri S, D'Incau P, et al. Adverse drug reaction reporting by nurses: analysis of Italian pharmacovigilance database. *Pharmacoepidemiology and drug safety*. 2012;21(6):597-602.
55. Rosli R, Dali AF, Aziz NA, et al. Reported Adverse Drug Reactions in Infants: A Nationwide Analysis in Malaysia. *Frontiers in pharmacology*. 2017;8:30-30.
56. Criado PR, Criado RFJ, Maruta CW, et al. Histamine, histamine receptors and antihistamines: new concepts. *Anais brasileiros de dermatologia*. 2010;85(2):195-210.
57. de Vries TW, van Hunsel F. Adverse drug reactions of systemic antihistamines in children in the Netherlands. *Archives of disease in childhood*. 2016;101(10):968-970.
58. Doña I, Moreno E, Pérez-Sánchez N, et al. Update on Quinolone Allergy. *Current Allergy and Asthma Reports*. 2017 2017/07/27;17(8):56.
59. Niedrig D, Maechler S, Hoppe L, et al. Drug safety of macrolide and quinolone antibiotics in a tertiary care hospital: administration of interacting co-medication and QT prolongation. *European Journal of Clinical Pharmacology*. 2016 2016/07/01;72(7):859-867.

60. Salehifar E, Ala S, Amini M, et al. The role of Clinical Pharmacists in the improvement of a pharmacovigilance system: A review of the reported adverse drug reactions during 2004-2010 in Mazandaran Province of Iran. *Journal of Pharmaceutical Care*. 2013;8-12.
61. Jung IY, Kim JJ, Lee SJ, et al. Antibiotic-Related Adverse Drug Reactions at a Tertiary Care Hospital in South Korea. *BioMed Research International*. 2017 2017/12/31;2017:4304973.
62. Giardina C, Cutroneo PM, Mocciaro E, et al. Adverse Drug Reactions in Hospitalized Patients: Results of the FORWARD (Facilitation of Reporting in Hospital Ward) Study [Original Research]. *Frontiers in Pharmacology*. 2018 2018-April-11;9(350).
63. Chan SL, Ang X, Sani LL, et al. Prevalence and characteristics of adverse drug reactions at admission to hospital: a prospective observational study. *British Journal of Clinical Pharmacology*. 2016;82(6):1636-1646.
64. Mandavi, D'Cruz S, Sachdev A, et al. Adverse drug reactions & their risk factors among Indian ambulatory elderly patients. *Indian J Med Res*. 2012;136(3):404-410.
65. Ognibene S, Vazzana N, Giumelli C, et al. Hospitalisation and morbidity due to adverse drug reactions in elderly patients: a single-centre study. *Internal Medicine Journal*. 2018;48(10):1192-1197.
66. Davies EC, Green CF, Taylor S, et al. Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes. *PLoS One*. 2009;4(2):e4439.
67. Safari M, Zandian Z, Vakili S, et al. Adverse drug reactions causing admission to a Pediatric Hospital in Hamedan–Iran: a 2 years study. *Iranian Journal of Pharmacology and Therapeutics*. 2015;13(1):26-0.
68. Hatam N, Askarian M, Moravveji AR, et al. Economic burden of inappropriate antibiotic use for prophylactic purpose in shiraz, iran. *Iran Red Crescent Med J*. 2011;13(4):234-238.
69. Askarian M, Maharlouie N. Irrational Antibiotic Use among Secondary School Teachers and University Faculty Members in Shiraz, Iran. *Int J Prev Med*. 2012;3(12):839-845.
70. Gholami K, Babaie F, Shalviri G, et al. Pediatric hospital admission due to adverse drug reactions: Report from a tertiary center. *J Res Pharm Pract*. 2015 Oct-Dec;4(4):212-215.

Tables

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Systems most commonly associated with adverse drug reactions at two hospitals in Iran. * Skin and subcutaneous tissue disorders; ** General disorders and administration site conditions; *** Respiratory, thoracic and mediastinal disorders; **** Metabolism and nutrition disorders; ***** Injury, poisoning and procedural complications; ***** Eye disorders and Psychiatric disorders.

Figure 2

Drug-classes most commonly associated with adverse drug reactions in two hospitals in Iran *Anti-infectives for Systemic Use; ** Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins; *** Use various drug classes; **** Antineoplastic and Immunomodulating Agents.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary.docx](#)
- [Tables.pdf](#)