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The evaluation of adverse drug reactions in Saudi Arabia: A retrospective observational study

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ABSTRACT

Purpose: This study aimed to assess the type, severity, seriousness, reasons, and outcomes of adverse drug reactions (ADRs) in the reports submitted to the regional spontaneous ADR database.
Methods: A retrospective observational study was conducted to analyze all the Tabuk Health Affairs hospitals in Saudi Arabia submitted to SFDA from January 2020 to December 2020. The database was structured according to the Saudi ADR form's fields. The Naranjo algorithm was used to assess the causes of the ADRs (sFDA, 2022).
Results: For 1 year, 2,349 ADR reports, along with 242 suspected drugs for 4,114 reactions, were submitted to SFDA. We found more males than females had ADRs (56.1% vs. 43.8%, $P < 0.05$).

Antimicrobial drugs (26.9%), hematologic drugs (19.7%), and neuropsychiatric drugs (12.9%) were responsible for most ADRs. Most of the reactions were associated with the use of ciprofloxacin (7.7%), followed by the combination of lopinavir and ritonavir (4.1%). Two deaths resulted from salbutamol and cefazolin use. Based on the results of the Naranjo assessment of causality, cardiovascular events (9.9%) exhibited the highest score (≥9) for a causal relationship with the suspected drugs, followed by dermatological events (9.5%).
Conclusions: The spontaneous report database is an important and valuable source of aftermarket authorization safety information. In our study, most drugs used as antimicrobial, cardiovascular, and hematologic therapies were associated with a higher risk of developing severe and serious events. We recommend monitoring and using medications optimally to ensure patient safety.

1. Introduction

The World Health Organization (WHO) defined "Pharmacovigilance" as "The science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems." In 1961, after the thalidomide disaster, the WHO established its International Drug Monitoring Program in Uppsala at the country level. The American Society of Health-System Pharmacists defined an adverse drug reaction (ADR) as a nonpreventable adverse drug event that occur during the usual use of medication (Lee et al., 2022).

The spontaneous reporting system is the most widely used system that pharmaceutical companies, health care professionals, and patients use to report ADRs detected during treatment. These reports are submitted to the national authorities that regulate pharmacovigilance activities in the country.

Collecting spontaneous adverse events from health care providers or patients in a regional database helps to monitor medication

Abbreviations: ADR, Adverse drug reaction; KSA, The Kingdom of Saudi Arabia; MOH, The Saudi Ministry of Health; RDIC, Regional Drug Information Center; WHO, The World Health Organization; SFDA, Saudi Food and Drug Authority.

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safety and assist in the responsible organization of investigation into the signals associated with ADRs and drug use (Prasanth et al., 2020).

In 2009, the Saudi Food and Drug Authority (SFDA) was established as a national pharmacovigilance center to collect spontaneously reported ADRs via email, fax, phone, and electronic submissions. The national pharmacovigilance center is a full member of the WHO's Uppsala Monitoring Center (Alshammari et al., 2019).

From its inception, the national pharmacovigilance center began implementing the pharmacovigilance concept and applying activities in its hospitals and clinics in cooperation with the Ministry of Health (Thiesen et al.,) and other health sectors. At the end of 2018, The Health Affairs in the Tabuk region took a proactive step at the level of all regions to sign an agreement with the Saudi Food and Drug Authority that included four hospitals and the Regional Drug Information Center (RDIC). Furthermore, we have a coordinator who submits reports from the hospitals and their primary care centers in each hospital. At the same time, The RDIC plays many roles, such as supervising hospitals' performance in the adverse drug reporting system, establishing risk minimization programs, analyzing the reports, performing the proper safety evaluation, ensuring sustainable enabler for medication safety culture, and other activities related to pharmacovigilance in Tabuk health affairs hospitals under the SFDA umbrella.

This study aimed to assess the types, seriousness, outcomes, and causes of ADRs submitted to the regional spontaneous ADR database. In addition, this study discusses strategies for improving the reporting of ADRs among health care professionals and consumers.

2. Methods

We conducted a retrospective observational study to analyze all ADR reports the Tabuk Health Affairs hospitals in Saudi Arabia submitted to SFDA from January 2020 to December 2020.

The database was structured according to the Saudi ADR form's fields, which are similar to the MedWatch ADR form. The data included information about the patient, drug, event, and reporter (sFDA, 2022).

The basic patient information included age, sex, past medical history, and past drug history.

Each event report contained the following information on the reactions: duration, description, seriousness, times at which the event started and ended, duration of the suspected drug use, and reaction outcomes if the patient did not recover or if the reaction was not resolved. The report also included actions (e.g., stopping the drug, reducing or increasing the dose, or making other changes to the dose) and a causality assessment (e.g., rechallenge/dechallenge or drug-reaction matrix; normally, if different drugs are associated with different events in same patient, then different case reports are filed).

All ADRs were assessed for causality using the Naranjo algorithm, which is the most commonly used tool to assess ADR reasons. This algorithm contains 10 simple questions that are answered as "yes," "no," or "do not know" in the following areas: the temporal relationship, the pattern of response, dechallenge or the administration of an antagonist, rechallenge, alternative causes, placebo responses, the drug level in body fluids or tissue, the dose–response relationship, the patient's previous experience with the drug, and confirmation via other objective evidence. The answer to each question receives a score. The total score ranges from −4 to 13. A score of 9 or more indicates a definite ADR, a score of 5 to 8 indicates a probable ADR, a score of 1 to 4 indicates a possible ADR, and doubtful if 0 or less (Murayama et al., 2018). The patient outcomes were reported as recovered or not recovered.

Additionally, we assessed which organ system the adverse reaction affected, the pharmacological classifications of the products involved, and the route of administration.

The ADRs' severity was classified into hospitalization, required intervention to prevent permanent impairment or damage, disability occurring (disruption in the patient's body function/structure, physical activities, or quality of life), required monitoring, or death.

The comparative demographic and categorical variables were presented as frequencies (percentages) to achieve readily comparable information and quantify. At the same time, we calculated gender-specific incidence. All data were analyzed using Statistical Analysis Software, version 9.4.

3. Results

We analyzed spontaneous reports by collecting 2,349 reports of ADR cases for 4,114 reactions From January 2020 to December.The age group with the greatest number of patients (n = 519, 12.6%) was 41–50, followed by the group of patients aged 31–40 (n = 491, 11.9%), as shown in Table 1.

The majority of the studied population was male (n = 1320, 56.1%; female: n = 1029, 43.8%). Death occurred equally for both sexes. Nevertheless, among males, ADRs were more severe. We found males had ADRs that were more life-threatening (n = 8, 0.61%) and caused prolonged hospital stay (n = 590, 44.7%) or hospitalization (n = 169, 12.8%) more often when compared to females (n = 3, 0.29%, n = 296, 28.82%, n = 50, 4.8%, respectively), as shown in Fig. 1.

Two patients in the 50 and older group died due to ADR, and most of the life-threatening adverse reactions were associated with patients older than 60. Of the reactions, 96.69% of patients recovered, as shown in Tables 1 and 2.

The antimicrobial category had the greatest number of suspected drugs associated with ADRs (n = 633, 26.9%), followed by hematological drugs (n = 461, 19.7%) and neuropsychiatric drugs (n = 301, 12.9%), as shown in Fig. 2.

Hematological and antimicrobial drugs led to four (0.17%) life-threatening cases. Hematologic drugs caused patient hospitalization in 2.3% of cases. Prolonged hospitalization was associated with the use of antimicrobial drugs (n = 280, 11.9%). Two deaths resulted from salbutamol and cefazolin use, as shown in Fig. 2.

Drugs resulting in the greatest number of ADRs were ciprofloxacin (7.7%) and the combination of lopinavir and ritonavir (4.1%). In 3,978 cases (96.7%), patients with reactions recovered, and only 128 (3.1%) did not recover. Most patients with ciprofloxacin-induced reactions recovered (n = 280, 6.8%), and (n = 36, 0.9%) did not recover ($P < 0.05$), as shown in Table 3.

The most frequently observed systemic events with a score of 9 or more, determined using the Naranjo causality assessment, were cardiac events (9.9%), dermatological events (9.5%), and renal events (7.5%). A score of 9 or greater indicates a highly probable adverse reaction, as shown in Table 4. The highest medication reported as definite adverse event was ciprofloxacin (n = 198, 4.8%) followed by clarithromycin (n = 122, 2.97).

Gastrointestinal events (630; 15.3%) were the most common systemic event medication use caused in patients who often recovered, followed by hepatic events (516; 12.5%), as shown in Table 4.

4. Discussion

The present study found a relationship between older age and a more frequent number of ADRs, in contrast with other studies that extensively argued for the lack of relationship between older age

Table 1
Adverse event incidence rate with different age groups.

Age	Death		Disability		Hospitalization		Life threatening		Needed interventions		Prolonged hospitalization		Total 4114	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0–10	0	0	0	0	11	0.3	0	0	98	2.4	79	1.9	188	4.6
11–20	0	0	0	0	0	0	0	0	9	0.2	5	0.1	14	0.3
21–30	0	0	2	0.05	14	0.3	1	0.02	124	3.01	90	2.2	233	5.7
31–40	0	0	0	0	52	1.3	3	0.07	252	6.1	178	4.3	491	11.9
41–50	0	0	2	0.05	53	1.3	0	0	254	6.2	210	5.1	519	12.6
51–60	1	0.02	0	0	42	1.02	3	0.07	225	5.5	162	3.9	431	10.48
61–70	0	0	0	0	31	0.8	3	0.07	165	4.01	103	2.5	302	7.34
71–80	1	0.02	0	0	14	0.3	1	0.02	76	1.85	51	1.2	144	3.5
81–90	0	0	0	0	1	0.02	0	0	15	0.36	5	0.12	21	0.5
> 90	0	0	0	0	0	0	0	0	9	0.21	1	0.02	10	0.2

and ADRs (Beijer and de Blaey, 2002, Pillans, 2008). Many factors could make this age group more susceptible to ADRs, such as comorbidities, the inappropriate use of a prescription, insufficient monitoring, and polypharmacy (Lavan and Gallagher, 2016).

Regarding the association between sex and adverse drug events in contrast to our findings, Rademaker et al. (2001) found females had a 1.5 to 1.7 times greater risk of experiencing ADRs compared to males (Rademaker, 2001). However, Aljadhey from Saudi Arabia and Thiesen from the United Kingdom did not report a significant difference in ADR experiences among patients who were stratified based on sex (Thiesen et al., 2013, Aljadhey et al., 2016). But Holm's study from Sweden showed that males reported experiencing ADRs that were more serious compared to females, which reflects our results (Holm et al., 2017).

In the present study, antimicrobial agents ranked the highest in terms of causing ADRs, which is consistent with other studies conducted locally and internationally. For example, a study in the Kingdom of Saudi Arabia (KSA) identified antibiotics as the most frequently implicated drugs in ADRs (Khan et al., 2012). Furthermore, studies conducted in Italy and India revealed antimicrobial drugs caused the greatest number of ADRs (Patidar et al., 2013, Salvo et al., 2013, Mudigubba et al., 2018).

Antimicrobial drugs are commonly prescribed in the KSA, which might explain the higher number of adverse events observed for this drug class. One Saudi study that confirms this explanation revealed that antibiotics were the most commonly prescribed drugs in the KSA (AlKhamees et al., 2018). However, this trend might diminish in the KSA in the future. In 2018, the MOH announced new enforcement of the Executive Regulations of Health Practice Law that prohibit dispensing antibiotics without a prescription to regulate antibiotic use, especially that of community pharmacies. In addition, the MOH warned that those who dispensed antibiotics without a prescription would be fined up to SR100,000 (26,654 $) (AlRukban and AlRuthia, 2020).

Furthermore, antibiotic stewardship programs have already been established in some hospitals in the KSA and have been effective in decreasing the overwhelming number of prescriptions for antibiotics, thus ensuring the rational prescription of antimicrobials. The expectation of a decrease in antimicrobial-related adverse events in the future, due to the previously mentioned advancements, should be investigated in future studies comparing the frequency of ADRs before and after implementing the new regulations (Alawi and Darwesh, 2016).

Two studies have highlighted the incidence of dermatologic events associated with use of ciprofloxacin (Mandal et al., 2004, Ada and Yilmaz, 2008). In the present study, we found ciprofloxacin-related ADRs ranged from skin hypersensitivity lesions to more systemic serious events, such as increased levels of transaminase enzymes, kidney injuries, severe hypotension, tachycardia, and convulsions.

As shown in Giardina, the most frequently used medications associated with ADRs were antibacterial agents (38.2%), followed by antithrombotic agents (21.7%). Among the antibiotic agents, quinolones (18.5%) and the penicillin group (7.0%) were the most frequently involved drugs (Giardina et al., 2018). These results paralleled ours.

We reported skin reactions and hepatic events with lopinavir and ritonavir. The reasons for the increased adverse events of this combination may be related to extensive use during 2020 due to its addition to the therapeutic protocol for treating COVID-19 patients in KSA. Similarly, this also happens with hydroxychloroquine, and most reactions were neurological reactions, cardiac events, and hepatic events. In addition, Cortegiani reported that high dosages of hydroxychloroquine as well as comorbidities and combinations with macrolides might increase adverse cardiac events (Cortegiani et al., 2020).

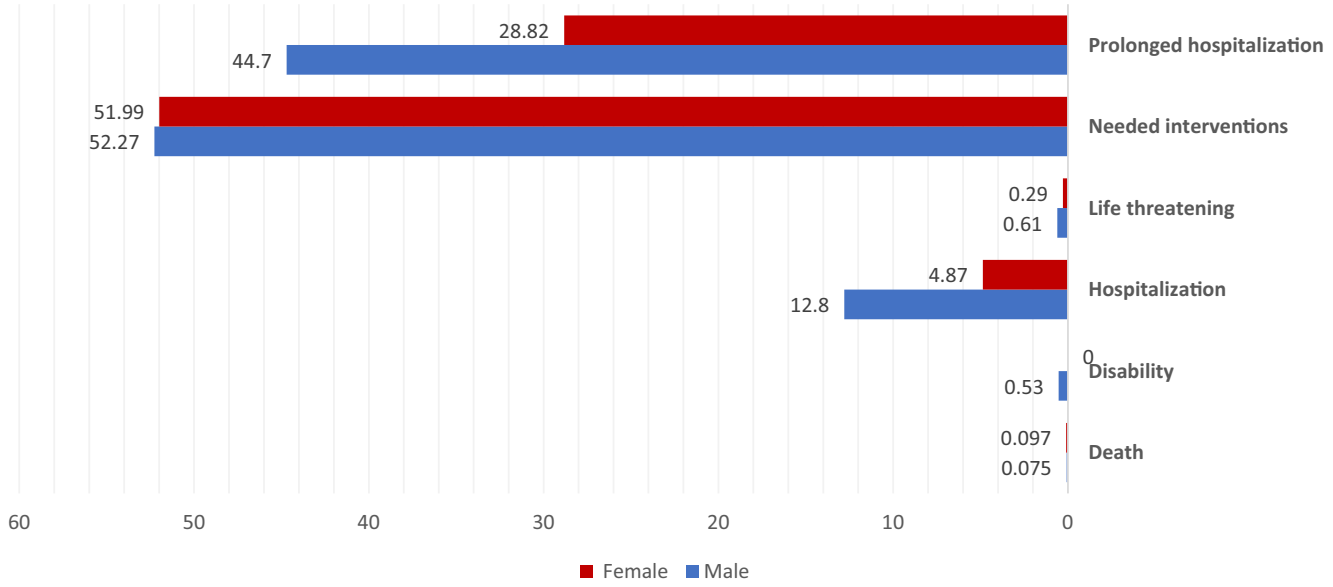

Fig. 1. Evaluation of gender-specific incidence and seriousness of adverse events.

Table 2
Adverse events outcome among different age groups.

Age	Recovered		Did Not Recover		Unknown		Fatal	
	N	%	N	%	N	%	N	%
0–10	174	4.22	5	0.12	0	0	0	0
11–20	84	2.04	3	0.07	2	0.04	0	0
21–30	599	14.5	7	0.17	0	0	0	0
31–40	675	16.4	12	0.29	0	0	0	0
41–50	768	18.6	9	0.21	0	0	0	0
51–60	544	13.2	10	0.24	1	0.024	1	0.024
61–70	894	21.7	22	0.53	0	0	0	0
71–80	197	4.78	32	0.77	1	0.024	1	0.024
81–90	33	0.8	24	0.58	0	0	0	0
>90	10	0.24	4	0.09	0	0	0	0
Total	3978	96.69	128	3.1	4	0.09	2	0.04

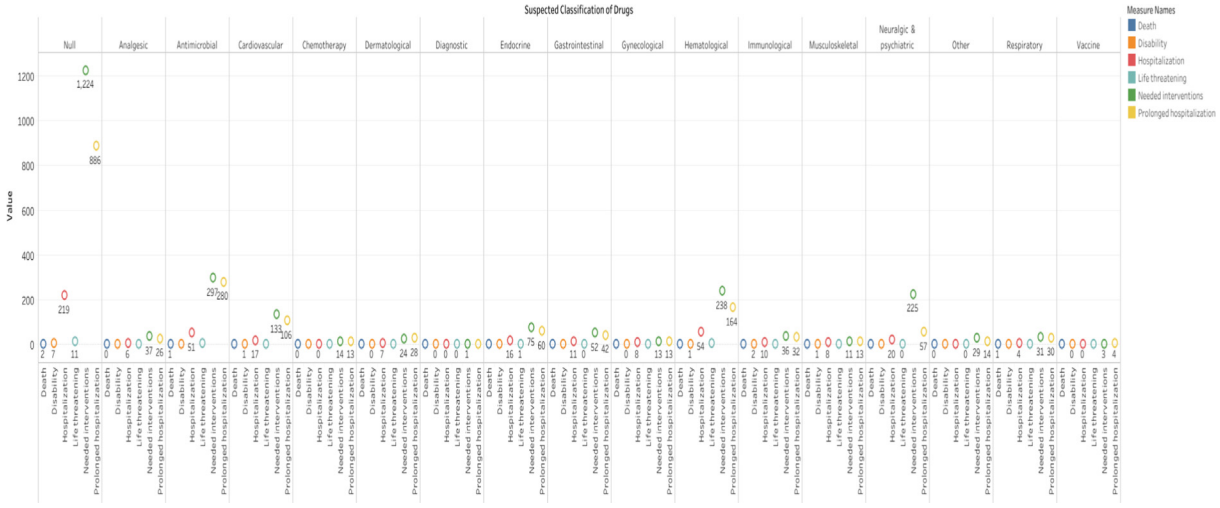

Fig. 2. Association between the classification of drugs and seriousness of adverse events.

In Lombardi study conducted in Italy, 28.66% of the reported ADRs were severe and 26.86% led to hospitalization (Lombardi et al., 2018), which is similar to our findings. Likewise, our results were consistent with those Cortegiani 2020, where almost all patients experiencing ADRs recovered and improved (94.9%). Burggraaf warned of the sudden death of asthma patients during

Table 3
Top ten suspected drugs causing adverse drug reactions.

Suspected Drug	Recovered		Did Not Recover		Total Reactions N = 4114	
	N	%	N	%	N	%
Ciprofloxacin	280	6.8	36	0.87	316	7.7
Lopinavir 200 mg + Ritonavir 50 mg	166	4.03	2	0.048	168	4.1
Metformin Hydrochloride	146	3.5	14	0.34	160	3.9
Amoxicillin, Clavulanic Acid	152	3.6	7	0.17	159	3.8
Clarithromycin	149	3.6	6	0.14	155	3.78
Moxifloxacin	149	3.6	4	0.09	153	3.7
Levofloxacin	140	3.4	5	0.12	145	3.5
Isotretinoin	126	3.06	8	0.19	134	3.2
Fingolimod HCl	106	2.5	24	0.58	130	3.15
Hydroxychloroquine Sulfate	55	1.3	10	0.24	65	1.6

Table 4
Association between systemic events, the Naranjo causality scale score and outcome of adverse events.

Systemic event	Possible*		Probable**		Definite***		Outcome								Total 4114	
	N	%	N	%	N	%	Recovered		Did Not Recover		Unknown		Fatal		N	%
							N	%	N	%	N	%	N	%		
Cardiovascular	20	0.48	46	1.12	411	9.99	444	10.7	32	0.8	1	0.02	1	0.02	477	11.6
Dermatological	17	0.41	80	1.94	394	9.58	467	11.35	24	0.6	0	0	0	0	491	11.9
Endocrinological	10	0.24	39	0.95	290	7.05	328	7.9	11	0.3	0	0	0	0	339	8.2
Gastrointestinal	65	1.58	286	6.95	279	6.78	619	15.04	10	0.24	1	0.02	0	0	630	15.3
Gynecological	10	0.24	10	0.24	33	0.8	53	1.3	0	0	0	0	0	0	53	1.3
Hematological	30	0.73	68	1.65	194	4.72	263	6.4	29	0.7	0	0	0	0	292	7.1
Immunological	3	0.07	5	0.12	62	1.51	64	1.6	5	0.12	0	0	1	0.02	70	1.8
Neurological & Psychiatric	17	0.41	17	0.41	263	6.39	285	6.92	10	0.24	2	0.05	0	0	297	7.2
Ophthalmic	0	0	7	0.17	62	1.51	69	1.7	0	0	0	0	0	0	69	1.8
Respiratory	6	0.15	40	0.97	176	4.28	221	5.4	0	0	0	0	0	0	222	5.3
Musculoskeletal	12	0.29	44	1.07	99	2.41	153	3.7	2	0.05	0	0	0	0	155	3.8
Renal	38	0.92	66	1.60	310	7.54	410	9.9	4	0.1	0	0	0	0	414	10.1
Hepatic	46	1.12	190	4.62	280	6.81	513	12.5	3	0.07	0	0	0	0	516	12.5
Other	16	0.39	40	0.97	33	0.80	89	2.2	0	0	0	0	0	0	89	2.2
Total	290	7.05	938	22.8	2886	70.15	3978	96.7	128	3.1	4	0.1	2	0.05	4114	100

Possible*: 1 to 4 points, Probable**: 5 to 8 points, Definite***: 9 points or more.

hypoxia associated with beta-2 adrenoceptor agonists, whereas death occurred in our study due to salbutamol use in one case (Burggraaf et al., 2001).

A Saudi interventional study found 10% of the reported ADRs were definite. At the same time, the remaining ADRs were possible or probable (Alshammari et al., 2015), and these results differ from ours. Most ADRs were definitely related to antimicrobial, hematological, neurological, and cardiovascular drugs. In addition, the prescribers typically had extensive experience with these medications, which increases the relative ease of identifying any adverse event and relating it to the drug used.

We also found that the most definite ADRs associated with cardiac events were related to fluoroquinolones and macrolides. These results were similar to Postma's study findings: Cardiac events occurred in 3.8%, 2.6%, and 4.1% of patients exposed to ciprofloxacin, levofloxacin, and moxifloxacin, respectively, and in 5.3%, 7.2%, and 11.2% of patients exposed to azithromycin, clarithromycin, and erythromycin, respectively (Postma et al., 2019).

In the present study, the gastrointestinal system includes the most frequently affected organs, followed by liver and skin reactions, and most of these events related to the use of metformin and metronidazole. On the other hand, fluoroquinolones, isotretinoin, and fingolimod HCl induced hepatic reactions. However, according to the literature, the gastrointestinal system includes the most frequently affected organs, followed by the liver (Kourorian et al., 2009).

In this context, a study found that patients exposed to fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) had a 20% increased likelihood of developing hepatotoxicity relative to persons who were not exposed to these agents (Alshammari et al., 2014). Additionally, liver test abnormalities occurred in up to 15% of patients on isotretinoin. However, marked elevations above three times the upper limit of normal or that require drug discontinuation are rare. Another study found a statistically significant increase in low-density lipoprotein and triglyceride levels in patients undergoing isotretinoin treatment (Kizilyel et al., 2014).

We applied several strategies to increase the number of ADR reports, such as establishing guidelines for monitoring, detecting, preventing, and reporting ADRs; providing education activities; promoting awareness campaigns; increasing motivation; establishing the role of a medication safety officer; increasing the participation of clinical pharmacists in rounds with physicians; allowing pharmacists to act immediately on ADR recognition; establishing medication counseling; establishing clinic and reconciliation programs; providing periodic ADR feedback reports to health care providers; establishing risk minimization programs for specific medications; and using social media to improve awareness.

Finally, based on our findings, efforts to minimize the occurrence of adverse drug events should be dedicated to achieving the safest and most effective drug therapies.

Likewise, pharmaceutical companies in the KSA need to understand the importance of implementing pharmacovigilance in a well-resourced department that can perform complete pharmacovigilance activities. The activities should also be applied according to the SFDA guidelines and regulations. Moreover, governmental and private hospitals that have not yet established

pharmacovigilance centers should establish them and incorporate the role of medication safety officers.

We suggest that integrating health information systems can help promote developing methods for detecting ADRs.

More important, patients using drugs known to cause life-threatening ADRs should be evaluated and monitored continuously. Similarly, older patients should also be prioritized in screening and monitoring because this group has a higher risk of developing ADRs. Moreover, we should not underestimate the importance of motivating pharmacists to understand their essential roles in decreasing the rate of ADRs through educating patients about the possible ADRs associated with suspected medications. In addition, patients should be educated about the available methods for reporting ADRs.

4.1. Study limitations

To our knowledge, this study is the first to explore the issue of ADRs in the Tabuk region. The present study revealed a high rate of ADRs in the region. However, some limitations are worth mentioning. First, this retrospective study was based on reports from patients and health care providers and not on clinical observations and judgments. Thus, the ADRs might have been underreported and the symptoms that occurred with the drug being used might have been misjudged. In addition, some patients might have underlying conditions that could contribute to the presence of a complaint or finding. However, this limitation is common in any ADR survey, even prospectively designed studies. Second, the study targeted the population in the Tabuk region, and thus, the results are not generalizable to the Saudi population.

4.2. Conclusions

The regional spontaneous report database strengthens the importance and role of ADRs in monitoring the safety information of marketed drugs and their value related to investigating the signs associated with ADRs. Frequently used medications are associated with a higher risk of developing severe and serious events, especially antimicrobials, cardiovascular, and hematologic drugs. Therefore, education activities and campaigns regarding strategies to identify and report any suspected ADRs are essential to avoid underreporting adverse drug events. In addition, the reported high rate of ADRs might be significantly reduced through the cooperation of health authorities, health care professionals, hospitals, pharmaceutical companies, and the public.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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