

Prevalence of Cutaneous Adverse Drug Reactions According to Iraqi Pharmacovigilance Center; A retrospective study for 11 years (2010-2021)

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Abstract :

Background: Cutaneous Adverse Drug Reactions (CADRs) are among the leading causes of morbidity and mortality. Insufficient data exists on cutaneous adverse reactions, as many of these reactions are not reported due to their constantly changing patterns and the interaction of multiple risk factors.

Aim: This study aims to evaluate the prevalence of cutaneous reactions in Iraq and find the most commonly involved active ingredients with the commonest skin manifestations.

Method: A retrospective study based on the safety reports of patients having cutaneous reactions that were collected and submitted to Vigibase by the Iraqi Pharmacovigilance Center between 2010 and 2021. The study involved the analysis of gender, age, medicines, type of CADR, and seriousness of more than 4,300 reports.

Results: Skin rash was the most commonly reported CADR, and antibiotics were the leading drug class; ceftriaxone and vancomycin were responsible for 40.3% and 16.2% of the cases caused by antibiotics only, respectively. The mean age of the patients was 28 years, and the male-to-female ratio was 0.78:1. Out of the total number of cases, more than 1300 were deemed serious, and 15 patients have passed away.

Conclusion: Iraq comes in the 51st place among other countries in the number of skin and skin-related ADR cases. Older adults are at higher risk of developing serious CADRs. Ceftriaxone and rash were the leading drug and cutaneous manifestations, respectively.

Keywords: Cutaneous Adverse Drug Reactions, Iraqi pharmacovigilance center, Vigibase, VigiLyze.

انتشار التفاعلات الدوائية الضارة المؤثرة على الجلد طبقاً للمركز العراقي لليقظة الدوائية؛ دراسة بأثر رجعي لمدة ١١ عاماً (٢٠١٠-٢٠٢١)

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الخلاصة:

التفاعلات الجلدية التي يسببها الدواء هي من بين الأسباب الرئيسية للمراضة والوفيات. مع أنماطها المتغيرة باستمرار، وتفاعل عوامل الخطر المتعددة، وبما أن غالبية ردود الفعل هذه لا تزال غير مبلغ عنها، لا توجد بيانات كافية تتعلق بالتفاعلات الضارة الجلدية.

تهدف هذه الدراسة إلى تقييم مدى انتشار هذه التفاعلات في العراق وتحديد أبرز الأدوية المسببة لها مع المظاهر الجلدية الأكثر شيوعاً. تم عمل دراسة بأثر رجعي تستند إلى تقارير السلامة للمرضى الذين يعانون من ردود فعل جلدية والتي تم تقديمها إلى المركز العراقي لليقظة الدوائية بين عامي ٢٠١٠ و ٢٠٢١. تضمنت الدراسة تحليل الجنس والعمر والأدوية ونوع التفاعل الجلدي وخطورة أكثر من ٤,٣٠٠ تقرير.

كانت المضادات الحيوية هي فئة الأدوية الرائدة المسببة لهذه التفاعلات، وكان السيفترياكسون والفانكوميسين مسؤولين عن ٤٠,٣٪ و ١٦,٢٪ من الحالات، على التوالي. كان متوسط عمر المرضى ٢٨ عاما وكانت نسبة الذكور إلى الإناث ٠,٧٨:١. تم تقييم أكثر من ١٣٠٠ حالة على أنها خطيرة، وتضمنت ١٥ حالة وفاة. ويأتي العراق في المرتبة ٥١ بين الدول الأخرى في عدد حالات الجلد والتفاعلات الدوائية المرتبطة بالجلد. وجد ان كبار السن هم أكثر عرضة للإصابة بحالات تفاعل جلدية خطيرة. وكان السيفترياكسون هو أكثر مادة دوائية تم التبليغ عنها والطفح الجلدي هو أكثر تفاعل جلدي تم التبليغ عنه

الكلمات المفتاحية: التفاعلات الدوائية الضارة، تفاعلات جلدية ضارة، المركز العراقي لليقظة الدوائية.

Introduction

Cutaneous adverse drug reactions (CADRs) are unanticipated changes in skin structures or functions that occur in response to medications ^(1,2). CADRs comprise about one-third of all drug reactions, ranging from simple self-limiting to severe life-threatening reactions ⁽³⁾. Severe cutaneous reactions (SCARs) are estimated by the World Health Organization (WHO) to be around 2% of all CADRs ⁽⁴⁾, and despite the rarity of these severe reactions, the mortality and morbidity rates are high ⁽⁵⁾.

Antibiotics are among the most common drugs that cause CADRs, especially as they are responsible for nearly half of the instances. Other risk factors for CADRs include female gender, age, infections, genetic and environmental factors ^(6,7).

There is insufficient data regarding cutaneous reactions, as most remain unreported. This is due to the fact that the vast majority of these reactions go undetected, and their patterns are changing continuously with the introduction of new medications ⁽⁸⁾.

Pharmacovigilance (PV) is essential for establishing the safety profile of the drugs that are available commercially ^(9,10). PV relies mainly on two methodologies, active and passive (spontaneous) monitoring, and even though the latter has its own limitations, but is crucial for the early detection of new or changed risks ⁽¹¹⁾.

In order to determine the prevalence of these adverse responses in Iraq and to identify the most offending medicines, this study was designed. This will aid in a better understanding of these adverse reactions and facilitate their quick and effective

management, minimizing the impact on the healthcare system.

Method

A retrospective observational study in which VigiLyze was used to acquire all the CADRs' reports from January 2010 through December 2021 of Iraqi patients that were collected and submitted to VigiBase by the "Iraqi Pharmacovigilance Center (IPhVC)". The study included 4371 individual case safety reports (ICSRs) and gender, age, symptoms, type of CADR, and medicines involved were analyzed.

VigiBase is the WHO database based on spontaneous surveillance ⁽¹²⁾. In VigiBase, the adverse events are coded utilizing the preferred term (PT) in the "Medical Dictionary for Regulatory Activities" (MedDRA) terminology, and the active ingredients are standardized according to WHO Drug and coded according to "Anatomical Therapeutic Chemical" (ATC) classification system ⁽¹³⁻¹⁵⁾. VigiLyze is a tool that allows access to VigiBase and analyzes its data ⁽¹⁶⁾.

The seriousness of cases was evaluated according to WHO seriousness criteria ⁽¹⁷⁾:

- cause permanent or significant disabling
- causes a congenital anomaly
- life-threatening
- requires intervention to prevent permanent impairment or damage
- requires or prolongs hospitalization
- fatal

Statistical Analysis

Descriptive statistics were calculated using IBM SPSS version 27 and graphs were

prepared using Microsoft Excel Professional Plus 2021.

Results

The study found that there were over 27,000 ICSRs. Out of these, 4,371 were CADR,

and by comparing these findings with all global cases in VigiLyze during the same time period, the percentage of CADR in Iraq was found to be slightly lower, as shown in Table 1.

Table 1. Cases of ADRs submitted to VigiBase between 2010 and 2021

	Global (Total)	Iraq
Total ADR cases	24,171,514	27,140
ADRs in Skin and subcutaneous tissue	4,176,548	4,371
Percentage of skin and skin-related ADRs	17.28%	16.1%

ADR, Adverse Drug Reaction

The mean age for these patients was 28.12 years, ranging from newborn to 100 years, and the largest proportion of patients was in

the (18-44) age group (Figure 1), with a female preponderance by a male-to-female ratio of 0.78:1 (Figure 2).

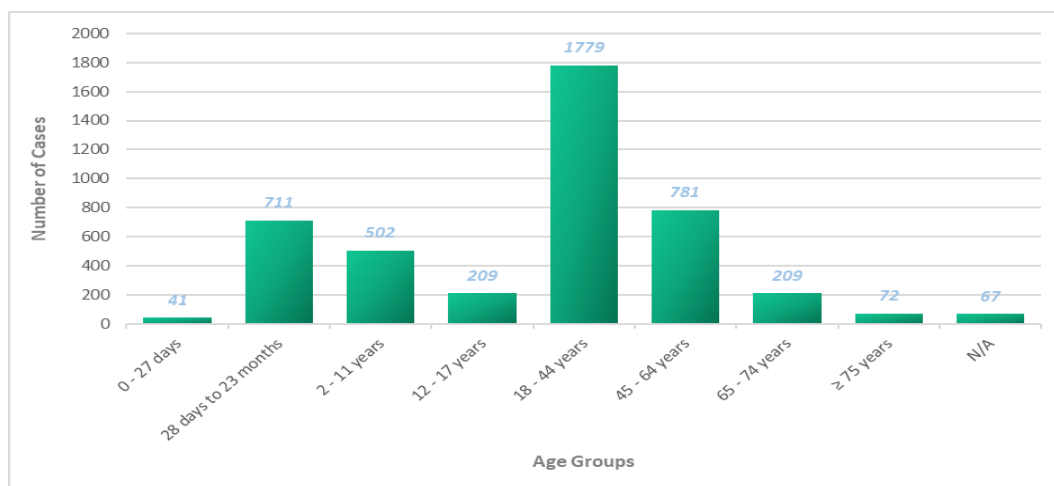


Figure 1. Number of reported CADR distribution based on age groups in Iraq between 2010 and 2021. N/A, not available.

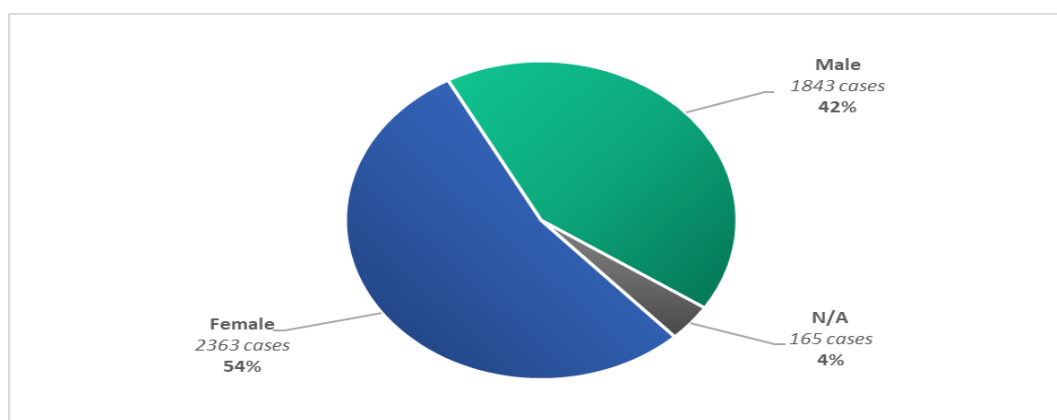


Figure 2. Percentage of reported cutaneous reaction cases based on gender in Iraq between 2010 and 2021. N/A, not available.

The reactions involved 416 offending active ingredients, and 103 different skin reactions were reported in the aforementioned period. Antibiotics were the leading incriminating drug group, with ceftriaxone being the most

commonly reported antibiotic associated with cutaneous reactions (Figure 3), and rash being the most common skin reaction (Figure 4).

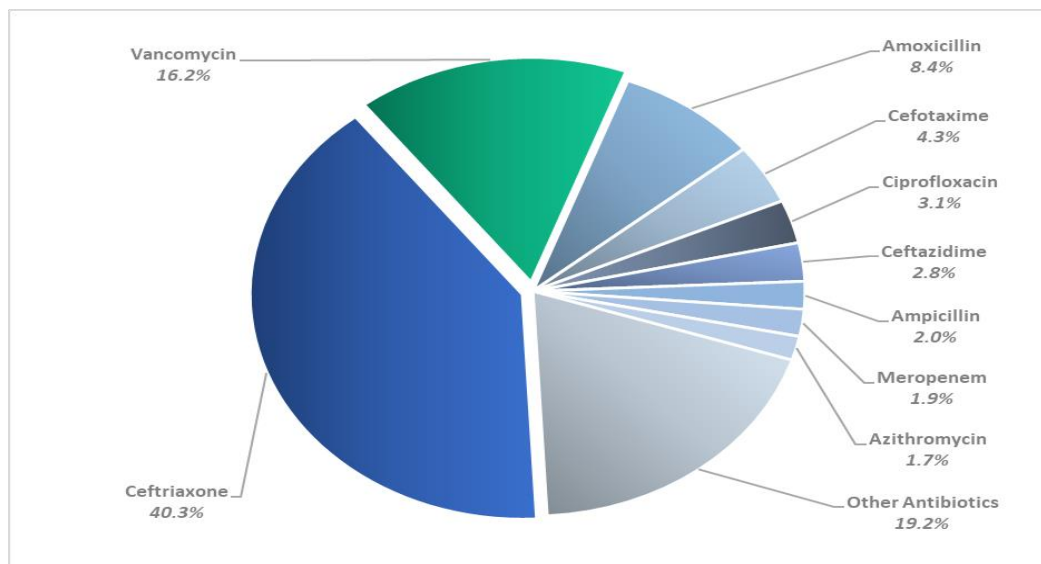


Figure 3. The leading antibiotics reported causing CADR in Iraq between 2010 and 2021

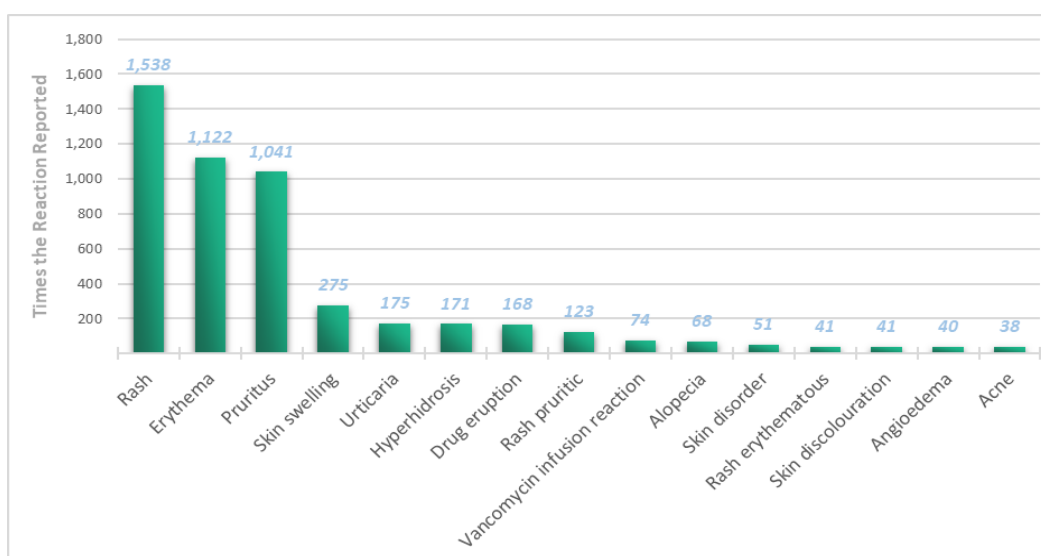


Figure 4. The most commonly reported cutaneous reaction in Iraq between 2010 and 2021

About one-third of the cases were serious, and the reactions caused 15 deaths (1.1% of serious reactions); the distribution of the serious cases over the different seriousness

criteria is shown in Figure 5. Tables 2 and 3 show that the likelihood of having a serious reaction is significantly associated with age and gender.

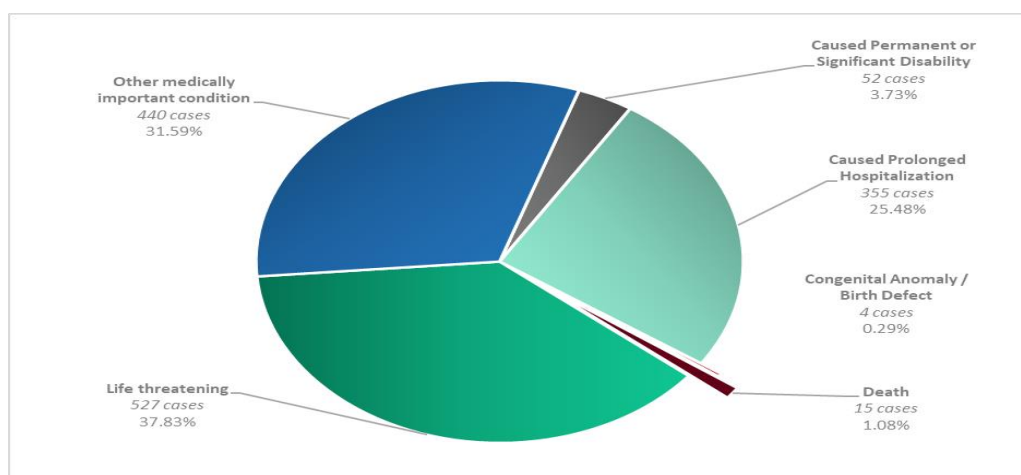


Figure 5. Serious cases distributed according to WHO seriousness criteria

Table 2. Age groups of Iraqi Patients with CADR between 2010 and 2021 according to seriousness

Age Group	Not Serious (%) (N=2738)	Serious (%) (N=1352)	Total	P-Value
0 - 27 days	31 (79.5%)	8 (20.5%)	39	< 0.001
28 days to 23 months	494 (77.4%)	144 (22.6%)	638	
2 - 11 years	304 (63.2%)	177 (36.8%)	481	
12 - 17 years	128 (64.0%)	72 (36.0%)	200	
18 - 44 years	1164 (68.0%)	548 (32.0%)	1712	
45 - 64 years	461 (61.3%)	291 (38.7%)	752	
65 - 74 years	121 (60.5%)	79 (39.5%)	200	
≥ 75 years	35 (51.5%)	33 (48.5%)	68	

Data presented as (N) number, (%) percentage. A chi-square test was performed for categorical data, and a P-value <0.05 is considered significant.

Table 3. Gender of Iraqi Patients with CADR between 2010 and 2021 according to seriousness

Gender	Not Serious (%) (N=2738)	Serious (%) (N=1352)	Total	P-Value
Female	1501 (65.4%)	794 (34.6%)	2295	0.018
Male	1237 (68.9%)	558 (31.1%)	1795	

Data presented as (N) number, (%) percentage. A chi-square test was performed for categorical data, and a P-value <0.05 is considered significant.

Discussion

Drug-induced SCARs are associated with morbidity, mortality, healthcare costs, and drug development challenges. Despite their rarity, SCARs can be fatal and create serious, potentially persistent complications (5).

Cutaneous reactions count for 10 to 15 percent of all reported ADRs (18), and by analyzing the reports submitted to Vigibase, it was found that the percentage

of CADR in Iraq was comparable. The most commonly reported reaction was rash, which coincides with the study of Natalia *et al* on the Polish population (19), a review article by Sapna *et al* on the Indian population (20), and a study by Ayesha *et al* (21). Erythema is the second most commonly reported, which differs from the previously mentioned studies.

In this study, the most offending class of drugs was antibiotics which agrees with

studies by Sapna *et al* ⁽²⁰⁾ and Mahmood *et al* ⁽²²⁾, and the leading causative active ingredient was Ceftriaxone which agrees with the studies by Fanping *et al* ⁽²³⁾ and Niharika *et al* ⁽²⁴⁾, while other studies noted Amoxicillin and Vancomycin as the leading offending antibiotics in Fatma Akpınar and Emine Dervis study and Julia *et al* study, respectively ^(25,26). Moreover, the leading causative agents were Anticonvulsants in Rojas *et al* study ⁽²⁷⁾ and NSAIDs in Shaik *et al* study ⁽²⁸⁾.

The variation in pattern and severity of these reactions depends on geographical and ethnic differences and the drugs used ⁽²⁹⁾. In the current study, Ceftriaxone, a 3rd generation cephalosporin, was the leading causative drug in Iraq because it is widely used in hospitals, as physicians frequently prescribe it as a first-line antibiotic, and outpatients, as Ceftriaxone is being heavily misused being readily accessible. Cephalosporins are β -Lactam antibiotics that are common causes of immediate and delayed hypersensitivity reactions, it is hypothesized that immunogenicity depends on the R1 side chain and the β -lactam moiety covalently bind to host proteins as Cephalosporins are small molecules and incapable of triggering an allergic reaction on their own ⁽³⁰⁾.

Since all sorts of reactions can be brought on by cephalosporins, and the rash is the most frequently observed side effect ^(30,31), consequently, the rash was the most commonly reported cutaneous reaction in Iraqi patients.

The largest age group, 18-44 years, formed about 40% of all cases, and it is comparable to other studies in Turkey, Iran, and India ^(22,24,25,32,33). This study found a statistically significant association between age and the likelihood of having a serious cutaneous drug reaction that agrees with a study in Germany which found older adults, age ≥ 65 years, are more often prone to having serious drug reactions ⁽³⁴⁾. The elderly population being vulnerable to serious cutaneous reactions is probably due to age-related changes in the pharmacokinetics and

pharmacodynamics of the drugs, multimorbidity, and polypharmacy; these factors are also considered risk factors for developing ADRs in the elderly by other studies ^(35,36).

The probability of having a drug-induced reaction is higher in the female gender and that was proved by several studies in China, Turkey, Korea, and other countries ^(20,23,31,33,34,37-39) including the present study that found that the number of Iraqi females having CADR is 30% higher than males, it is supposed to be caused by anatomical and physiological differences that include body weight, body composition, variables associated with the gastrointestinal tract, liver metabolism, and renal function, added to these, females consume drugs more frequently than males ⁽²⁵⁾. These variances can affect the drugs' pharmacokinetics and pharmacodynamics, resulting in different responses to the drugs ^(23,38).

Incomplete reports and under-reporting were the main limitations of this study, as they affect both the quality and quantity of reporting for potential ADRs that are fundamental to the spontaneous reporting system.

Conclusion

Age and gender are significant determinants of the probability of having a cutaneous drug reaction, older adults are at increased risk of having serious drug reactions and females are at higher risk of developing skin reactions.

The reactions ranged from simple skin rash to life-threatening and even fatal, with skin rash being the most commonly reported CADR. Ceftriaxone and Vancomycin were responsible for about one-third of the antibiotic-induced cutaneous reactions.

Under-reporting of ADRs affects how the benefits and risks of medications are assessed, especially when spontaneous reports are the sole or primary source utilized to make this determination.

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