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Research Article

Mortality Rate Related to Adverse Drug Reactions in Iraqi Patients: A Study Based on WHO Database

Ahmed Sami[1]*, Mohammed Mahmood Mohammed[2], Manal Mohammed Younus[3]

[1]*Baghdad Teaching Hospital, Medical City, Baghdad 10011, Iraq;* [2]*Department of Clinical Pharmacy, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq;* [3]*Iraqi Pharmacovigilance Center, Ministry of Health, Baghdad, Iraq*

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Abstract

Background: Adverse drug reactions (ADRs) are unintended harmful effects caused by medications that can occur at any dose. ADRs are a significant contributor to hospital admissions and are responsible for numerous fatalities, particularly among older adults with multiple chronic illnesses who take multiple medications. Reporting ADRs is critical for identifying the harmful effects of medications and monitoring patients in hospitals. ***Objective***: ADRs have a significant impact on mortality rates, but no previous studies in Iraq have focused on death-related reports. To address this problem, we conducted a study to assess mortality rates associated with ADRs in Iraq and identify the drugs most frequently involved. ***Methods***: We collected the ADR reports of Iraqi patients that were registered as fatal from January 2010 to January 2024 in The World Health Organization (WHO)pharmacovigilance database, VigiBase. The case-non-case method will be used to investigate the reporting risk in Iraq versus the rest of the world. ***Results***: A total of 329 fatal ADRs were found, and the mean age of affected patients was 36 years, with a male-to-female ratio of 1.25:1. Antineoplastic agents ranked first among drugs that caused fatal ADRs (38.4%), and pembrolizumab was the leading active ingredient (27 cases, 6.85%). ***Conclusions***: This study is the first to identify and describe fatal ADRs in Iraq and found them less common in Iraq, and the risk is lower in Iraqi women compared to Iraqi men.

Keywords: Adverse drug reaction, Iraq, Mortality, Pharmacovigilance.

معدل الوفيات المرتبطة بالتفاعلات الدوائية الضارة لدى المرضى العراقيين: دراسة تستند إلى قاعدة بيانات منظمة الصحة العالمية

الخلاصة

الخلفية: التفاعلات الدوائية الضارة (ADRs) هي آثار ضارة غير مقصودة تسببها الأدوية التي يمكن أن تحدث في أي جرعة. تعد ADRs مساهما كبيرا في دخول المستشفى وهي مسؤولة عن العديد من الوفيات، لا سيما بين كبار السن المصابين بأمراض مزمنة متعددة والذين يتناولون أدوية متعددة. يعد الإبلاغ عن ADRs أمرا بالغ الأهمية لتحديد الآثار الضارة للأدوية ومراقبة المرضى في المستشفيات. **الهدف**: تؤثر نتائج ADRs بشكل كبير على معدلات الوفيات، ولكن لم تركز أي دراسات سابقة في العراق على التقارير المتعلقة بالوفيات. لمعالجة هذه المشكلة، أجرينا دراسة لتقييم معدلات الوفيات المرتبطة ب ADRs في العراق وتحديد الأدوية الأكثر شيوعا. **الأساليب**: قمنا بجمع تقارير الأعراض الجانبية للمرضى العراقيين التي تم تسجيلها على أنها مميتة في الفترة من كانون الثاني 2010 إلى كانون الثاني 2024 في قاعدة بيانات منظمة الصحة العالمية لليقظة الدوائية, VigiBase. تم استخدام طريقة عدم وجود حالة للتحقيق في مخاطر الإبلاغ في العراق مقابل باقي دول العالم. **النتائج**: تم العثور على ما مجموعه 329 ADRs قاتلة، وكان متوسط عمر المرضى المصابين 36 عاما، مع نسبة الذكور إلى الإناث 1.25: 1. احتلت الأدوية المضادة للأورام المرتبة الأولى بين الأدوية التي تسببت في ADRs قاتلة (38.4٪)، وكان بيمبروليزوماب في صدارتها (27 حالة ، 6.85٪). **الاستنتاجات**: هذه الدراسة هي الأولى التي تحدد وتصف ADRs القاتلة في العراق ووجدت أنها أقل شيوعا في العراق، والخطر أقل لدى النساء العراقيات مقارنة بالرجال العراقيين.

* ***Corresponding author***: Ahmed Sami, Baghdad Teaching Hospital, Medical City, Baghdad 10011, Iraq; Email: ahmed21289@uomustansiriyah.edu.iq

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INTRODUCTION

According to the World Health Organization (WHO), an adverse drug reaction (ADR) refers to any unintended, noxious response to a drug, which may occur at doses typically used for the prevention, diagnosis, or treatment of a disease [1,2]. ADRs are a significant cause of hospital admissions and a major public health concern, given the morbidity and mortality they induce, as well as their strain on healthcare systems [3,4]. ADRs are responsible for a significant number of annual deaths, ranking as the fourth leading cause of death in the United States, following heart disease, cancer, and strokes [5]. A study conducted in Sweden estimated that about 3%

of deaths in the general population were caused by ADRs [4], while in Iraq, a study found fatal ADRs constitute about 2.4% (9) of the cases that suffered a drug reaction in two hospitals [6]. Up to 80% of ADRs are predictable. However, around 20% of ADRs are unpredictable and not dose-dependent [7], which means that even a generally healthy person taking a prescription medication for a minor issue could experience a potentially life-threatening ADR [8]. Some of the risk factors associated with ADRs include female sex, advancing age, the use of multiple medications, immunosuppression, and autoimmune disorders [9]. Older adults, in particular, tend to have many risk factors that increase the likelihood of experiencing ADRs, such as multiple chronic conditions requiring treatment with multiple medications (polypharmacy) [10]. Although clinical trials are one of the most important sources for collecting safety information and characterizing medicine's risks, Reporting is particularly important for ADRs that are rare or that occur only after long-term use, as these types of ADRs are not likely to be identified in premarket clinical [11,12]. Pharmacovigilance centers heavily rely on health professionals' voluntary reporting of adverse drug reactions (ADRs). The detection and reporting of serious ADRs have become critical components of hospital monitoring and evaluation activities [13].ADRs have a significant impact on mortality rates. However, in Iraq, no studies have been conducted to investigate death-related reports associated with ADRs. To address this issue, we conducted a study to evaluate the mortality rates linked with ADRs in Iraq, compare our statistics to global ones, and identify the drugs that are most commonly involved.

METHODS

Study Design

A retrospective study analyzed data from VigiBase, the WHO pharmacovigilance database, to determine the mortality prevalence of drug reactions. The Iraqi database included around 39,000 ADR reports of Iraqi patients who experienced a drug reaction, and they were forwarded to the Uppsala Monitoring Centre (UMC) by the Iraqi Pharmacovigilance Center (IPhvC) between January 2010 and January 2024.

Eligibility Criteria

All ADRs that resulted in death (fatal ADRs) registered in VigiBase from January 2010 to January 2024 were included, excluding all duplicate reports. This study involved the descriptive analysis of active ingredients and their anatomical therapeutic chemical (ATC) classes, number, sex, and age. The second part involved using the case-non-case method to investigate the reporting risk of fatal ADRs in Iraq compared to the rest of the world. We use this method to compare the proportion of drug exposure in cases associated with a specific adverse reaction to that of non-cases [14]. Fatal cases refer to the cases registered as "fatal" in VigiBase, while non-instances refer to all other reports documented in the same period without the death outcome. This approach helps to identify pharmacovigilance signals by analyzing the disproportionality of ADR reports in databases. The term "signal" is used in pharmacovigilance to refer to reported information that suggests a possible link between an adverse event and a drug. This link may not have previously been known or fully documented [15,16]. Results are presented as reporting odds ratios (ROR) [17], and we also used the information component (IC) to measure the strength of the relationship. IC is a logarithmic measure of disproportionality that is used for detecting signals of drug adverse reactions [18].

Ethical Consideration

The study adhered to the standards adopted by the Iraqi Ministry of Health as indicated by the 'Research Committee of the National Center for Training and Human Development' in the Ministry of Health & Environment, approval number 27 on February 19, 2024.

Statistical analysis

We utilized information components (IC) and reporting odds ratios (ROR) to demonstrate disproportionality. ROR is a ratio that is conceptually similar to the odds ratio used in case-control studies. If the ROR 95% confidence interval (ROR025) exceeds 1, and the IC 95% confidence interval (IC025) shows a positive value, it implies a higher frequency of reported fatal ADRs in Iraq compared to other regions of the world. This cutoff value is significant for each parameter. We calculate ROR and IC using the formulas listed in Table 1.

Table 1: Disproportionality analysis equations [19–22]

Parameter	Formula	Criteria
S	$\sqrt{1/A + 1/B + 1/C + 1/D}$	---
ROR	$\frac{A/B}{C/D}$	---
ROR_{025}	$e^{\ln ROR - 1.96 \times S}$	$ROR_{025} \geq 1$
IC	$\log_2 \frac{A \times (A+B+C+D)}{(A+B) \times (A+C)}$	---
IC_{025}	$IC - 3.3 \times \frac{1}{\sqrt{A+0.5}} - 2 \times \frac{1}{\sqrt{(A+0.5)^3}}$	$CI_{025} \geq 0$

A: Cases exposed to the drug of interest; B: Non-cases exposed to the drug of interest; C: Cases exposed to other drugs; D: Non-cases exposed to other drugs; IC: Information component; ROR: Reporting odds ratio; S: Standard deviation.

RESULTS

Over a period of 14 years, VigiBase received 39,883 deduplicated reports, of which 329 (0.82%) resulted in fatalities, a rate lower than the global reporting rate of ADR-caused deaths at approximately 4%. Figure 1 illustrates the annual number of ADRs and the corresponding percentage of fatal ADRs in Iraq.

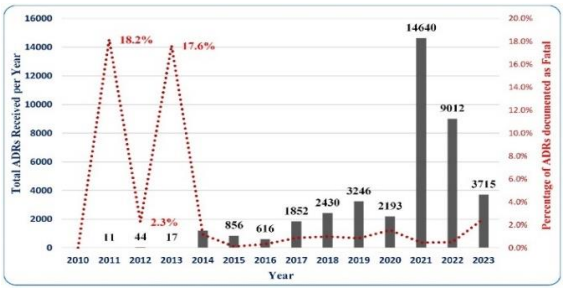

Figure 1: ADR reports received between January 2010 and January 2024 with the proportion of ADRs registered as Fatal per each year.

Figure 2 reveals a male preponderance, with a male-to-female ratio of 1.25:1 (173:138).

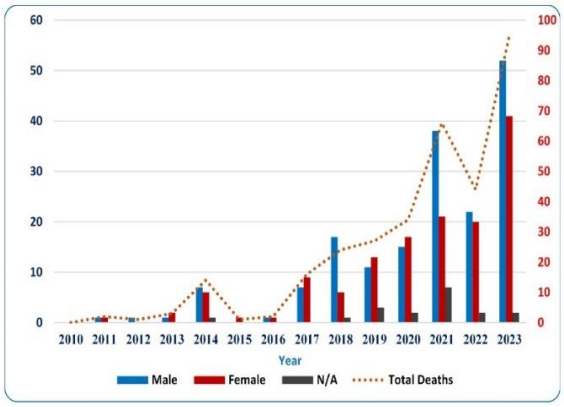

Figure 2: Drug-related deaths in Iraq distribution by sex. N/A: no available information on patient sex.

The mean age was 35.87 years (ranging from 1 day to 103 years old), and the most affected age group was 18–44 years, followed by the 45–64 year age group, with the age group distribution shown in Figure 3. The risk of reporting fatal ADRs in Iraq is lower than in the rest of the world, with a ROR of 0.20 and a ROR of 0.25 equal to 0.18, while the IC_{025} value was negative, -2.468, which reflects that this relation is not significant.

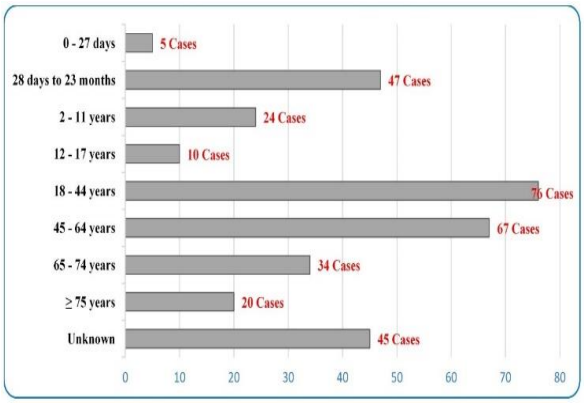

Figure 3: ADR-caused deaths distribution according to age groups between 2010 and 2024.

However, in Iraq, the risk of reporting fatal ADRs in males is slightly higher than the global rate. On the other hand, Table 2 lists the values for females, who had a slightly lower risk.

Table 2. Risk of reporting fatal ADRs in Iraq compared to that in global reports

ROR_{025} compared to Global Reporting	Value*
Overall (all Iraqi patients)	0.178
Males in Iraq	1.531
Females in Iraq	0.995

* a value of 1 for ROR_{025} is the cutoff value. ROR_{025} lower band of the 95% confidence interval of the ROR (reporting odds ratio).

Figure 4 shows that the most common types of suspected ATC were anticancer and immunomodulators (pembrolizumab, sorafenib), anti-infective drugs for systemic use (ceftriaxone, COVID-19 vaccine), and drugs that affect the digestive tract and metabolism. Pembrolizumab, ceftriaxone, and sorafenib were the top three drugs in terms of number of fatal ADRs. Table 3 lists the twenty drugs that caused the most fatal ADRs.

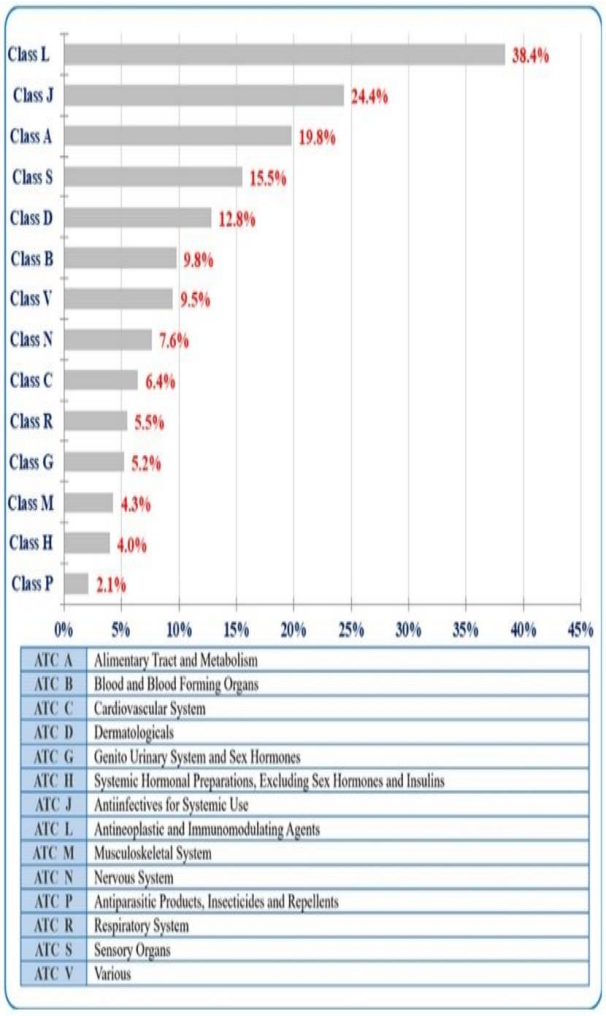

Figure 4: ADR-caused deaths distribution according to ATC drug class. ATC: Anatomical Therapeutic Chemical.

DISCUSSION

According to our research, the mortality rate caused by drug reactions is lower in Iraq compared to global statistics. Pembrolizumab is the primary active ingredient causing fatal ADRs.

Table 3. The leading suspected/interacting (S/I) active ingredients registered in fatal ADR reports in VigiBase between 2010 and 2024 (Percentage is from the total of 329 death cases)

Reported active ingredients (WHO Drug)	S/I n(%)
Pembrolizumab	27(6.85)
Sorafenib	21(5.33)
Ceftriaxone	17(4.31)
Covid-19 vaccine	17 (4.31)
Alglucosidase alfa	14(3.55)
Dexamethasone	12(3/05)
Cefotaxime	9(2.28)
Etanercept	8(2.03)
Rituximab	7(1.78)
Doxorubicin	7(1.78)
Alteplase	7(1.78)
Ramucirumab	7(1.78)
Polatuzumab vedotin	7(1.78)
Meropenem	6(1.52)
Diclofenac	6(1.52)
Interferon beta-1a	6(1.52)
Atezolizumab	6(1.52)
Enoxaparin	5(1.27)
Asparaginase	5(1.27)
Gemcitabine	5(1.27)

However, this study has some limitations related to its methodology. Like other pharmacovigilance studies, it is not intended to determine the actual prevalence of fatal ADRs. This is due to factors such as underreporting, selective reporting, or individual susceptibilities specific to each country. Pharmacovigilance databases are only useful to describe the primary features of ADR reports [23–26]. This study offers insights into drug-related deaths in Iraq from January 2010 to January 2024. The statistics demonstrate that pharmacists reported the highest number of individual case safety reports (ICSRs) (57.6%), while physicians came in second (26.5%). The study highlights the importance of pharmacists' role and knowledge structure in reporting ADRs, providing them with an advantage [27]. The Iraqi Pharmacovigilance Center became a part of the WHO International Drug Monitoring Program in 2010 [28]. After the SRS was developed in Iraq, the number of ICSRs and ICSRs with an outcome of death increased annually. Between 2010 and 2014, there was a notable increase in the proportion of death reports. This increase can be explained by the fact that during the initial stage of the SRS of Iraq, more attention was paid to the reports of serious cases and deaths, while the total number of annual reports was small. Other studies in China and the United States (US) showed a comparable pattern of variation in death report proportion [29,30]. Between 2016 and 2024, the percentages of death reports remained stable, reflecting a proportional increase in the number of death ICSRs reported with the total number of ICSRs. The supervisory authorities have pushed medical institutions, pharmaceutical manufacturers, and distributors to report more ICSRs, leading to increased reports of minor ADRs or external symptoms of related physical conditions. This has also resulted in a decrease in the proportion of serious or fatal ICSRs since 2014. The mean age was seen to be nearly half that in a study in Spain (74.9 years) by Pardo Cabello *et al*. [31] and another study in the US (59 years) by Marwitz *et al.* [29]; however, the most affected age groups were comparable to those in the Le *et al*. study [30]. According to the Montastruc et al. study [26], class L (antineoplastic and immunomodulating agents) was the leading ATC class. The leading drugs in this class were pembrolizumab and sorafenib. Regarding Pembrolizumab, anti-programmed death-1 (PD-1), there were 27 reports of related deaths, and all documented it as the solely administered active ingredient that was used for the treatment of non-small lung carcinoma in nearly all cases. A study of fatal adverse events revealed a 54% mortality rate due to immune-related events in response to anti-PD-1 agents [32]. Researchers linked Sorafenib, a protein kinase inhibitor, to an increased risk of fatal adverse events, mostly cardiac events [33,34]. Following antineoplastic, class J (antiinfective for systemic use) with Ceftriaxone and COVID-19 vaccines leading the class. Ceftriaxone is a commonly used medication in both inpatient and outpatient settings. It is generally well-tolerated by most individuals. However, it is the second most frequently reported drug associated with ADRs leading to death. This is likely due to its heavy usage, resulting in higher ADR reports than other active ingredients. The second and highest peak of COVID-19 infections and mortality was in 2021 [35]. Together with nearly six and a half million vaccinated Iraqis between March and October [36], both raised the proportion of fatal events related to COVID-19 vaccines.

Conclusion

This study is the first to identify and describe fatal ADRs in Iraq. In Iraq, the percentage of fatal ADRs and the likelihood of reporting them are generally lower than in the rest of the world. However, the risk of fatal ADRs is slightly higher for Iraqi men than the global average, as well as slightly higher for Iraqi men than for Iraqi women. To validate the current findings, additional research is required.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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