Kirkuk Journal of Medical Sciences

ORIGINAL ARTICLE

# Prevalence, Severity, and Predictors of Drug–Drug Interactions in Prescriptions from Sulaymaniyah, Iraq

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***Received:*** 08 July 2025
***Accepted:*** 13 October 2025
***First published online:*** 21 November 2025

**How to cite this article:**
Atiyah RS, Mohammed SF, Ismail HR, Abdullah TM. Prevalence, severity, and predictors of drug–drug interactions in prescriptions from Sulaymaniyah, Iraq. *Kirkuk Journal of Medical Sciences*. 2025;13(2):72-77.
DOI: 10.32894/kjms.2025.162574.1166

## ABSTRACT

**Background:** Drug–drug interactions (DDIs) represent a significant risk to patient safety, especially in settings where polypharmacy is common and decision-support systems are limited. This study aimed to assess the prevalence, types, mechanisms, and clinical predictors of potential drug–drug interactions in inpatient and outpatient drug prescriptions.

**Methods:** A cross-sectional study was conducted on 300 prescriptions collected from inpatient and outpatient departments in Sulaymaniyah city, between January and April 2025. The Medscape Drug Interaction Checker was used to identify and classify drug-drug interactions by severity (minor, moderate, major) and mechanism (pharmacokinetic, pharmacodynamic, or both). Associations with polypharmacy, gender, and care setting were analyzed using appropriate statistical analysis.

**Results:** Potential drug-drug interactions were identified in 81 prescriptions (27.0%), with a total of 148 interactions. Polypharmacy was strongly associated with drug-drug interaction occurrence: patients with five or more medications had significantly higher odds of drug-drug interactions (OR = 9.24; 95% CI: 4.31–19.78; $p < 0.001$), which increased further for those prescribed six or more drugs (OR = 16.25; 95% CI: 7.67–34.42). Most drug-drug interactions were moderate in severity (51.3%) and primarily pharmacodynamic in nature (57.4%). Gender and care setting were not significantly associated with drug-drug interaction risk.

**Conclusion:** Drug–drug interactions were common in Northern Iraq prescriptions, especially with polypharmacy, underscoring the need for better medication review and monitoring.

**Key words**: Polypharmacy; Drug-Drug Interactions; Pharmacodynamic Interaction; Medication Safety.

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## INTRODUCTION

Drug–drug interactions (DDIs) are a major concern in pharmacotherapy due to their potential to compromise treatment efficacy or result in serious adverse effects, including hospitalization and death [1, 2].

DDIs may be either pharmacokinetic or pharmacodynamic and may occur at any point during the treatment course. The clinical significance of DDIs is particularly higher in patients receiving multiple drugs, a scenario that is increasingly common in both inpatient and outpatient practice [3, 4].

Globally, the prevalence of potential DDIs ranges between 10% and 70%, depending on the clinical setting, population, and number of medications prescribed [5].

A recent meta-analysis revealed that around 60–80% of elderly patients in hospitalized settings are exposed to at least one potentially harmful drug interaction, particularly in the context of polypharmacy and multimorbidity [6].

Polypharmacy and inappropriate prescribing have been recognized globally as primary contributors to preventable medication-related harm in low- and middle-income countries, where clinical decision support aids and electronic prescribing systems are limited or absent [7].

In Iraq and other developing healthcare systems, inconsistencies in prescribing policies and underdeveloped clinical pharmacy services also heighten the risk of unrecognized DDIs [8]. Despite the growing attention to this issue, region-specific data on the prevalence, severity, and mechanisms of DDIs in Northern Iraq, particularly in Sulaymaniyah, remains scarce. Additionally, limited access to validated drug interaction databases in the majority of Iraqi hospitals is an obstacle to active DDI detection.

This study was conducted to bridge this gap by assessing the prevalence, types, and predictors of DDIs in prescriptions collected from inpatient and outpatient settings in Sulaymaniyah. Particularly, the study aimed to determine the association of DDIs with polypharmacy, care settings, gender, and to classify the mechanisms and clinical severity of the identified interactions according to one validated drug interaction database.

## MATERIALS AND METHODS

This cross-sectional study was conducted between January and April 2025 in Sulaymaniyah city, Iraq.

The study was carried out in two primary settings: the outpatient pharmacy department and the inpatient wards of large public hospitals (Baxshin, Shar, Mercy, Shorsh, Harem) in Sulaymaniyah city. A convenience sample of 300 prescriptions was obtained and analysed. Prescriptions used were for adults ($\geq$ 18 years old) who had at least two medications. Prescriptions were excluded if they were illegible or lacked complete drug information, such as name or dosage form. Prescriptions for herbal, nutritional, or non-pharmacological items, and duplicate or multiple prescriptions from the same patient during the study period were also excluded to avoid bias.

All prescriptions were scanned for possible DDIs using the Medscape Drug Interaction Checker (WebMD, USA), version 12.27.0, a tool that is frequently used in clinical practice [9].

DDIs were categorized by severity (minor, moderate, or major) and mechanism (pharmacokinetic, pharmacodynamic, or both).

This observational study did not involve patient interaction or experimental work. Data were imported into Microsoft Excel and analyzed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics (percentages, frequencies) tabulated patient characteristics and prescription attributes. Associations between categorically defined variables (e.g., polypharmacy and DDI presence) were investigated by using the Chi-square ($\chi^2$) test. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

All the statistical abbreviations and terms used are defined in their respective tables. No questionnaires were used in the study, and no clinical trial registration was required; it was a non-interventional study.

## RESULTS

This study involved a total of 300 prescriptions. As indicated in Table 1, the majority of patients were female, comprising 63.3% (n = 190) of the sample, while male patients represented 36.7% (n = 110). In the clinical setting, the prescriptions were mostly for inpatients (66.7%, n = 200), compared to 33.3% (n = 100) for outpatients. Regarding drug interactions, 81 prescriptions (27.0%) had at least one potential drug-drug interaction (DDI). A total of 148 DDIs were detected in all the prescriptions, indicating that there was more than one interacting drug pair in many prescriptions.

**Table 1.** Demographic and prescription characteristics (N = 300)

| Variable | n | % |
|---|---|---|
| **Gender** | | |
| Male | 110 | 36.7 |
| Female | 190 | 63.3 |
| **Setting of care** | | |
| Inpatient | 200 | 66.7 |
| Outpatient | 100 | 33.3 |
| **Drug–drug interactions (DDIs)** | | |
| Total DDIs identified | 148 | — |
| Prescriptions with $\geq$1 DDI | 81 | 27.0 |

Within the 300 prescriptions analyzed, acetaminophen (administered orally and intravenously) emerged as the most frequently prescribed medication, constituting 6.0% of the total drugs. This was followed by loratadine at 4.3% and diclofenac at 3.3%. Additional medications included metronidazole, dexamethasone, furosemide, enoxaparin, and ciprofloxacin. The tablet form was the predominant dosage form, representing approximately 53.5% of the top 10 drugs, while injectable forms comprised nearly 46.5% as shown in Table 2.

**Table 2.** Top 10 most frequently prescribed drugs (N = 300 prescriptions)

| Drug (dosage form) | n | % |
|---|---|---|
| Acetaminophen (IV injection; tablet) | 18 | 6.0 |
| Loratadine (tablet) | 13 | 4.3 |
| Diclofenac (tablet) | 10 | 3.3 |
| Metronidazole (IV injection) | 10 | 3.3 |
| Dexamethasone (IV injection) | 10 | 3.3 |
| Furosemide (tablet) | 9 | 3.0 |
| Enoxaparin (SC injection) | 9 | 3.0 |
| Ciprofloxacin (tablet) | 8 | 2.7 |
| Pregabalin (tablet) | 7 | 2.3 |
| Hydrocortisone (tablet) | 7 | 2.3 |

The number of drugs per prescription also varied widely, with two or three drugs being in most prescriptions (37.3% each). Polypharmacy, defined as $\geq$ 5 drugs per prescription [10], was observed in 12.7% (n=38). Only a small number of prescriptions contained ten or more drugs, and there was one prescription with up to seventeen drugs; further details are illustrated in Table 3.

**Table 3.** Distribution of number of drugs per prescription and prevalence of polypharmacy (N = 300)

| Number of drugs | n | % |
|---|---|---|
| 2 | 112 | 37.3 |
| 3 | 112 | 37.3 |
| 4 | 38 | 12.7 |
| 5 | 19 | 6.3 |
| 6 | 8 | 2.7 |
| 7 | 2 | 0.7 |
| 8 | 2 | 0.7 |
| 9 | 3 | 1.0 |
| 10 | 3 | 1.0 |
| 17 | 1 | 0.3 |
| **Polypharmacy** | | |
| $\geq$5 drugs | 38 | 12.7 |

Moderate DDIs were most frequent (76/148, 51.3%), followed by minor (52/148, 35.1%) and major (20/148, 13.5%). By mechanism, pharmacodynamic interactions predominated (85/148, 57.4%) over pharmacokinetic interactions (60/148, 40.5%); a small proportion involved both mechanisms simultaneously (3/148, 2.0%). Within pharmacodynamic DDIs, synergistic effects were most common (37.8%), followed by additive (11.4%) and antagonistic (8.1%) effects. Within pharmacokinetic DDIs, metabolism-related interactions were most common (27.0%), followed by absorption (10.13%), distribution (2.0%), and excretion (1.35%) as shown in Table 4.

**Table 4.** Severity and mechanism of potential drug–drug interactions (DDIs) (N = 148 interactions)

| Category | n | % |
|---|---|---|
| **Severity of DDI** | | |
| Major | 20 | 13.5 |
| Moderate | 76 | 51.3 |
| Minor | 52 | 35.1 |
| **Mechanism of DDI** | | |
| Pharmacodynamic | 85 | 57.4 |
| Pharmacokinetic | 60 | 40.5 |
| Both | 3 | 2.0 |
| **Pharmacodynamic subtype** | | |
| Synergistic | 56 | 37.8 |
| Additive | 17 | 11.4 |
| Antagonistic | 12 | 8.1 |
| **Pharmacokinetic subtype** | | |
| Metabolism | 40 | 27.0 |
| Absorption | 15 | 10.1 |
| Distribution | 3 | 2.0 |
| Excretion | 2 | 1.3 |

The association of prescription-related factors with the occurrence of DDIs is shown in Table 5. Polypharmacy was significantly associated with DDIs (OR = 9.24, 95% CI: 4.31–19.78; $p < 0.001$). Similarly, patients taking $\geq$6 drugs had a significantly higher risk compared with patients with 2–3 drugs (OR = 16.25, 95% CI: 7.67–34.42; $p < 0.001$). Gender and care setting (inpatient or outpatient) did not show any significant relationship with the occurrence of DDIs.

The ten most prevalent potential drug–drug interactions (DDIs) are summarized in Table 6. The most common pair was acetaminophen–metronidazole ($n$ = 8), which may increase hepatotoxicity via altered hepatic metabolism. The second most common was acetaminophen–enoxaparin ($n$ = 7), a pharmacodynamic interaction that may increase bleeding risk by augmenting anticoagulant effect. Other notable pairs were dexamethasone–loratadine ($n$ = 4), aspirin–folic acid ($n$ = 3), and candesartan–labetalol ($n$ = 3). Overall, most interactions were minor to moderate in severity and pharmacokinetic or pharmacodynamic in mechanism, with clinical effects ranging from changes in drug exposure to increased risks of bleeding, antagonism of sedation, or hypotension.

**Table 5.** Association between demographic/prescription factors and potential DDIs (odds ratios with 95% confidence intervals)

| Risk factor | With DDIs, % | Without DDIs, % | Odds ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Number of prescribed medications** | | | | |
| 2–3 drugs (Ref) | 18.7 | 81.2 | — | **< 0.001** |
| 4–5 drugs | 43.8 | 56.1 | 3.32 (1.84–5.98) | |
| ≥6 drugs | 78.9 | 21.0 | 16.25 (7.67–34.42) | |
| **Setting** | | | | |
| Inpatient (Ref) | 26.0 | 74.0 | — | 0.552 |
| Outpatient | 30.0 | 70.0 | 1.22 (0.72–2.08) | |
| **Polypharmacy** | | | | |
| Non-polypharmacy (<5) (Ref) | 21.0 | 79.0 | — | **< 0.001** |
| Polypharmacy (≥5) | 71.1 | 28.9 | 9.24 (4.31–19.78) | |
| **Gender** | | | | |
| Female (Ref) | 25.7 | 74.2 | — | 0.513 |
| Male | 30.0 | 70.0 | 1.23 (0.73–2.08) | |

Ref: reference category. Percentages are row-wise. Odds ratios compare each category with its stated reference.
En dash (–) is used for CI ranges; em dash (—) indicates not applicable.

**Table 6.** Top 10 most prevalent potential DDIs and their risk level

| No. | Drug interaction | n | Severity | Mechanism | Clinical effect |
|---|---|---|---|---|---|
| 1 | Acetaminophen–Metronidazole | 8 | Minor | Pharmacokinetic | Elevated hepatotoxicity risk due to interference with hepatic enzyme. |
| 2 | Acetaminophen–Enoxaparin | 7 | Minor | Pharmacodynamic | May enhance anticoagulant effects and increase bleeding risk. |
| 3 | Dexamethasone–Loratadine | 4 | Moderate | Pharmacokinetic | May reduce loratadine plasma concentration via CYP3A4 induction. |
| 4 | Aspirin–Folic acid | 3 | Minor | Pharmacokinetic | May reduce absorption of folic acid, lowering serum folate levels. |
| 5 | Candesartan–Labetalol | 3 | Moderate | Pharmacodynamic | Additive blood-pressure–lowering effect; may cause hypotension. |
| 6 | Caffeine–Diphenhydramine | 3 | Moderate | Pharmacodynamic | Caffeine may antagonize sedative effects of diphenhydramine. |
| 7 | Metronidazole–Ondansetron | 2 | Moderate | Pharmacokinetic | May increase risk of QT prolongation and arrhythmias. |
| 8 | Acetaminophen–Metoclopramide | 2 | Minor | Pharmacokinetic | May enhance absorption and peak levels of acetaminophen. |
| 9 | Etoricoxib–Hydrocortisone | 2 | Minor | Pharmacodynamic | Increased risk of gastrointestinal irritation or ulceration. |
| 10 | Hydrocortisone–Rabeprazole | 2 | Minor | Pharmacokinetic | May decrease rabeprazole levels via CYP3A4 metabolism. |

DDIs = drug–drug interactions. Mechanism/clinical-effect summaries are derived from the Medscape Drug Interaction Checker.

## DISCUSSION

Drug–drug interactions (DDIs) remain a pervasive and preventable threat to medication safety, particularly in contexts of polypharmacy [11].

In prescriptions from Sulaymaniyah, 27.0% contained at least one potential DDI, and polypharmacy (defined as ≥ 5 medicines) was the strongest predictor of risk. This aligns with existing literature, where polypharmacy (five or more medications) was the strongest DDI predictor as Kasim et al.(2023) [8], who reported a 57.6% prevalence of DDI in Nineveh, and Mijk KN et al. (2024) [12], who reported high rates of polypharmacy in elderly patients attending Duhok hospitals.

Alongside prevalence, mechanisms and intensity of interaction were thoroughly categorized. The majority were of moderate severity (51.3%), and pharmacodynamic mechanisms were the most common (57.4%), particularly synergistic effects. This finding is consistent with Ramadhani et al. (2023) [13], who also reported pharmacodynamic interactions as the most frequent among patients with geriatric type 2 diabetes mellitus, observing their potential impact on clinical outcomes and overall quality of life. Our results confirm the underemphasized potential of extensively co-prescribed drugs such as acetaminophen, metronidazole, and enoxaparin, highlighted by Vilar et al. (2012) [14], which are seen to be safe on their own but may pose risks when co-prescribed.

Furthermore, certain drug combinations observed in this dataset—such as dexamethasone–loratadine and candesartan–labetalol—are often clinically underemphasised yet may still influence patient outcomes. Similar, underreported DDIs have been documented in the literature; for example, Bourdin V et al. [15], and Eisenberg J et al. (2023) [16]

reported transient adverse effects related to lidocaine-based interactions.

Unlike earlier hypotheses, neither gender nor the context of care was a predictor of risk for DDI, consistent with the multicenter report by Aljadhey H et al. (2016) [17]. This finding aligns with the suggestion that prescription complexity, rather than patient profile, determines interaction frequency, as noted in the systematic review by Bories M et al. (2021) [18].

Despite our findings, our study faced several limitations. We lacked data on adverse drug events or clinical outcomes due to insufficient follow-up, hindering our assessment of the actual harm from the identified interactions. Additionally, we did not examine patient-specific factors like age, comorbidities, or organ function (e.g., renal/hepatic impairment) that could influence interaction risk. Moreover, using only one interaction-checker application and limiting our study to a single governorate may affect the generalizability of our results.

Future work should aim to integrate reviews by pharmacists, clinical decision support systems, and adjuvant therapy assessment to reduce interaction burden, as supported by existing evidence [19, 20]

## CONCLUSION

Possible DDIs were identified in 27% of screened prescriptions, mostly moderate and pharmacodynamic. Polypharmacy was the strongest predictor of DDI. Acetaminophen, metronidazole, and enoxaparin were the most commonly involved drugs. These findings highlight the need for routine interaction screening and vigilant prescription monitoring using drug interaction software and thorough review of the patient's full medication history.

## ETHICAL DECLARATIONS

- **Ethics Approval and Consent to Participate**

  The Scientific Research Ethics Committee, College of Medicine, Komar University of Science and Technology, approved the study (Approval No. 230905-123557; January 2025). The study used de-identified prescription data only and involved no direct patient contact.

- **Consent for Publication**

  None.

- **Availability of Data and Material**

  The datasets are available from the corresponding author upon reasonable request.

- **Competing Interests**

  The authors declare that there is no conflict of interest.

- **Funding**

  Self-funded.

- **Use of Generative Artificial Intelligence**

  The authors declare that no generative AI tools were used in the preparation, writing, or editing of this manuscript.

- **Authors' Contributions**

  All authors contributed to the literature review, study design, data collection, statistical analysis, and manuscript preparation. All authors have read and approved the final version of the manuscript.

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