RESEARCH ARTICLE

REVISED Assessment of potential drug-drug interactions in hospitalized patients with infectious diseases: an experience from a secondary care hospital

[version 4; peer review: 2 approved, 2 not approved]

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Abstract

Background

Polypharmacy is common among hospitalized patients with infectious infections owing to comorbidities or concurrent illnesses. This raises the likelihood of drug-drug interactions and creates uncertainty for healthcare providers. This study aimed to assess the potential drug-drug interactions (pDDIs) among hospitalized patients with infectious diseases in a secondary care hospital.

Methods

A prospective observational study was conducted in the internal medicine ward for six months. Data were collected from patient case records, and prescriptions were screened for pDDIs and classified based on the severity from a portable electronic physician information database (PEPID) resource analyzed using SPSS, version 27.0.

Results

In total, 148 patient case records were analyzed, and 549 pDDIs were

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identified, with 66.8% having at least one or more DDIs. The mean number of drug interactions was 3.70 ± 4.58 per prescription. The most frequently encountered drug interactions were drug combinations such as bisoprolol with atorvastatin and aspirin with tazobactam/piperacillin. Based on the severity, most pDDIs belong to the 'moderate' category (40.07%). Bivariate analysis showed that age, comorbidities, length of hospital stay, and the number of drugs prescribed were risk factors associated with DDIs ($p<0.05$). In the multiple binary logistic regression analysis, DDIs were significantly associated with comorbidities and the number of prescribed medications ($p<0.0001$).

Conclusions

This study observed the prevalence of DDIs in hospitalized patients with infectious diseases of 'moderate' severity. Prescription screening using a drug information database assists in identifying and preventing DDIs early, enhancing drug safety and quality of patient-centered care.

Keywords
Drug interactions, polypharmacy, prescription drugs, prevalence, patients

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 3**

The manuscript's organisation, clarity, and methodological rigour have all been improved with a number of significant revisions based on reviewer criticism. By eliminating references to statistical analysis and ethical committee permission, the abstract has been made more concise and now more directly addresses the objectives and conclusions of the study. The procedure for classifying drug-drug interactions (DDIs) according to severity levels has been made clear in the Methods section. Specifically, we have shown how to detect prospective DDIs (pDDIs) using the PEPID database and how these interactions are classified. The Results section also included a brief note on the severity levels of the most common DDIs.

The statement on data entry and analysis has been shifted to the Data Analysis section for improved organisation and to improve the manuscript's overall structure. To make several sections easier to read, we also consolidated them. "Infectious diseases" was used in the Introduction in place of "Infectious infections" to solve the terminology concern brought up by the reviewers. References were also included to support the Anatomical Therapeutic Chemical (ATC) categorisation scheme and the DDI severity classification.

For clarity, the table and figure have been updated. For example, Table 1's "SI No" column was eliminated, and the figure's quality was raised. We changed "Exp(B)" to "Adjusted OR" in Table 3 and included a footnote to make clear each DDI's Level of Concern and Source of Recommendation (SOR). In order to improve clarity, we also reworded some words. For example, we changed the Discussion section to emphasise the role that chemists play in managing DDI and to address the shortcomings of the PEPID database that was used for the study.

All things considered, the changes show a more structured, understandable text that more effectively responds to the reviewers' issues with terminology, methodology, and result interpretation.

Any further responses from the reviewers can be found at the end of the article

Introduction

Infectious diseases are among the most common health concerns globally, regardless of age. Infected people frequently require hospitalization, which increases the risk of morbidity and mortality and raises healthcare costs.[1] Infectious diseases are conditions caused by microscopic organisms such as bacteria, viruses, fungi, or parasites that spread from one person to another.[2] Healthcare providers frequently face challenges in selecting and using antimicrobial medicines.[3,4]

Drug-drug interactions (DDIs) occur when two or more co-administered drugs interact, with one drug altering the effect of the co-administered drug. The outcome effect of drug interactions may vary from non-serious to serious/life-threatening (or) irreversible, affecting the goals of therapy, clinical effectiveness, and worsening treatment outcomes.[5] Studies have reported that age (≥ 65 years), polypharmacy, increased number of prescribers, and comorbid illness are defined risk factors for drug interactions.[6,7] In addition, a decline in drug metabolism associated with aging, comorbidities such as hepatic and renal injury, and altered drug plasma concentrations complicate medication use and increase the sensitivity to drug interactions. As a result, clinically significant drug interactions prolong hospital stays, increase re-visit and healthcare expenditures, and aggravate patient outcomes in inpatient and outpatient healthcare settings.[8–10]

Drug interactions are classified as pharmacokinetic and pharmacodynamic interactions; a few are categorized as unknown or other based on their mechanism of interactions. Drug interactions can be grouped as major, moderate, or minor according to severity and significance.[11] Studies carried out in different health settings and patients reported that potential drug-drug interactions (pDDIs) range from 19.3% to 91.6%.[12,13] A systematic review and meta-analysis reported that the prevalence of clinically manifested DDIs ranged from 1.2% to 64.0%.[14] The increased incidence of adverse outcomes associated with drug-drug interactions is a common cause of hospital admission, primarily in the aging population.[15] However, the variation in the results across different studies is associated with factors such as patient characteristics, prescribing pattern, severity of the illness, study population, and study setting.

The use of clinical decision support systems, close monitoring of patient's drug therapy, and involvement of clinical pharmacists in a multidisciplinary team are some of the important measures that help to minimize drug interactions and improve patient safety.[16,17]

Studies on antimicrobial agents in the United Arab Emirates (UAE) have focused on the prescription pattern of drug use and related outcomes in various hospital settings. However, studies related to DDIs with antimicrobial agents in infectious diseases are unaddressed despite being one of the reasons for hospitalization. Therefore, the present study was carried out to assess pDDIs among hospitalized patients with infectious diseases in a secondary care hospital.

Methods

Study design and study setting

This prospective observational study was conducted from March 2021 to August 2021 in the internal medicine department of Ibrahim Bin Hamad Obaidullah Hospital in the northern Emirate of the United Arab Emirates.

Ethical approval

This study was performed per the principles outlined in the Declaration of Helsinki, the US Federal Policy for the Protection of Human Subjects (Common Rule), and the European Medicines Agency Guidelines for Good Clinical Practice.[18] Approval was obtained from the human ethics committee of Ras Al Khaimah Medical and Health Sciences University (RAKMHSU-REC-068-2020/21-UG-P) and the Research Ethics Committee of Ministry of Health & Prevention, Ras Al Khaimah (MOHAP/REC/2021/1-2021-PG-P) in January 2021.

After getting approval from the MOHAP-RAK REC, the principal investigator obtained written informed consent from all the patients who met the study criteria after explaining the study procedures and other details to the participants.

Inclusion criteria

Hospitalized patients aged 18 years and older who were diagnosed with infectious diseases caused by bacterial pathogens and received a minimum of two or more medications containing at least one antimicrobial agent were included in the study.

Exclusion criteria

Patients referred from other departments admitted to the intensive care unit, diagnosed with COVID-19 receiving antibiotics, with incomplete medical records, and pregnant or lactating were excluded from the study.

Sample size and sampling technique

The sample size was calculated using the formula to estimate a single proportion [$n = (Z - \alpha/2)^2\ p\ (1 - p)/d^2$] where Z = standard normal variable at 95% confidence level (1.96), p = the prevalence of pDDIs assumed to be 50% and finally adjusted using a correction formula. The minimum sample size was 150 patients with 5-10% dropouts. Patients admitted during the study period were considered for the sampling frame and included using the systematic random sampling technique.

Data collection

The medical records of the hospitalized patients who met the study criteria were reviewed daily. The data were collected from the Wareed system, an electronic health record information system (HIS), a technological platform that virtually connects all the government hospitals of ministry healthcare facilities in Dubai and the Northern Emirates by automating all healthcare processes across various departments. All necessary details of the patients, including drug therapy, were collected from the electronic health records and documented in the data collection form designed according to the needs of the study.

Assessment of drug-drug interactions

All prescription medicines were added to the 'drugs to check' list in the portable electronic physician information database (PEPID) interaction tool for evaluating pDDIs. (Pepid. LLC, 2024) The identified drug interactions were classified by level of concern as minor/non-significant, minor, moderate, significant, and life-threatening. They were also based on pharmacokinetics, pharmacodynamics, and other/unknown mechanisms.[19] The severity of interactions in PEPID is represented by colored warning triangles stacked in descending order. The number value within each triangle relates to the severity of the interaction, with a value of "5" indicating a potentially fatal circumstance, and the combination should never be employed. Level 4 implies a major interaction, which has a high risk of being severe or lethal. Contraindicated unless the benefits outweigh the hazards and no other choices exist. Level 3 indicates a moderate interaction, necessitating strict monitoring and the use of alternate drugs, if possible. Furthermore, level 2 implies a strong contact that requires close monitoring, whereas level 1 indicates a minimal or insignificant interaction.

Mechanism of interaction

Pharmacokinetic interactions can influence how medications are absorbed, transported, metabolized, and eliminated.

The term "pharmacokinetic drug interactions" describes modifications to a drug's distribution, metabolism, excretion, or absorption brought on by the presence of another medicine. Due to these interactions, drug concentrations in the body may change, raising toxicity or reducing therapeutic effectiveness. Typical processes include competition for protein binding, changes in the pH of the gastrointestinal tract, and inhibition or activation of enzymes.

Pharmacodynamic interactions occur when the effects of one drug are altered by the presence of another at its site of action, potentially resulting in synergistic or antagonistic therapeutic function or undesirable side effects. These interactions may result in unforeseen side effects, diminished (belligerent), or boosted (synergistic) effects. They can affect the drugs' overall therapeutic success and safety profile. They can result from comparable modes of action, opposing effects, or interactions at the same receptor sites.[19]

Data analysis

The class of medications involved in the onset of pDDIs was analyzed using the Anatomical Therapeutic Chemical (ATC) classification system derived by the World Health Organization.[20] The collected data were scrutinized and checked for completeness, clarity, and legibility before being entered into a Microsoft Excel (RRID: SCR_016137) spreadsheet and were later analyzed using IBM SPSS Statistics (RRID: SCR_016479) version 27 (IBM Corp., Armonk, NY, USA). Descriptive statistics, such as mean, standard deviation, frequencies, and percentages, were used to describe continuous data. Bivariate analysis using a chi-square test was used to identify factors associated with drug-drug interactions. In the binary logistic regression model, the related factors identified in the bivariate analysis ($p<0.05$) were entered, and the odds ratio and 95% confidence interval were used to determine the independent risk factors for pDDIs. Statistical significance was $p<0.05$.

Results

Patient demographics

In total, 148 hospitalized patient case records were included during the study period, with 77 (52.02%) males and 71 (47.97%) females. Most patients were in the 21–40 age range (28.37%), followed by 61-80 years (27.70%). The mean age was 54.27±24.3 (Mean±SD), ranging from 18 to 107 years.

Among the patients, more than half (56.76%) had a medical history of one or more comorbidities. The most common were cardiovascular diseases (40.88%) followed by diabetes mellitus (28.72%) and dyslipidemia (7.18%). Respiratory tract infection (34.83%), urinary tract infection (34.19%), sepsis (14.8%), and gastroenteritis (7.09%) were the most common infectious diseases for hospital admission in our study. Most hospitalized patients had a stay duration of 6-10 days (56.08%), and the average length of stay was 8.16±2.85 days (range: 3-16 days). In our study, the majority of patients (45.27%) received 6–9 drugs per prescription, and the average number of drugs per prescription was 8.35±3.19 (Mean±SD) (range: 2-16) medications (Table 1).[35]

Drug-drug interactions

In our study, 549 drug-drug interactions with 116 combinations of interacting drugs were observed. This includes 396 drug interactions from 64 non-antimicrobial combinations, 137 drug-drug interactions from 44 non-antimicrobial and antimicrobial combinations, and 16 drug-drug interactions from eight antimicrobial combinations. The mean drug interactions identified in the study population were 3.70±4.58 per prescription.

Table 1. Demographic details of the study population.

Variables	Categories	Frequency (%) (n=148)
Sex	Male	77 (52.02)
	Female	71(47.97)
Age (in years)	≤20	10 (6.75)
	21–40	42 (28.37)
	41–60	30 (20.27)
	61–80	41 (27.70)
	81 and above	25 (16.89)
Number of Comorbidities	Nil	64 (43.24)
	1–2	49 (33.10)
	3–4	31 (20.94)
	Five or more	4 (2.70)

Table 1. *Continued*

Variables	Categories	Frequency (%) (n=148)
Types of Comorbidities	Diabetes mellitus	52 (28.72)
	Cardiovascular	74 (40.88)
	Dyslipidemia	13 (7.18)
	Renal diseases	06 (3.31)
	Neurologic	13 (7.18)
	Thyroid	02 (1.10)
	Hematologic	02 (1.10)
	Gastrointestinal	05 (2.76)
	Respiratory	02 (1.10)
	Others: Benign Prostate Hypertrophy (n=2) Chronic Liver Disease (n=3) Osteoarthritis (n=1) Tuberculosis (n=05)	12 (6.62)
Diagnosis	Respiratory tract infection	54 (34.83%)
	Urinary tract infection	53 (34.19%)
	Sepsis	23 (14.83%)
	Gastroenteritis	11 (7.09%)
	Others: Pancreatitis (n=3) Pyelonephritis (n=2) Pelvic Inflammatory Disease (n=2) Meningitis (n=1) Enteric Fever (n=1) Diarrhea (n=2) Food Poisoning (n=2) Ascites (n=1)	14 (9.03%)
Hospital Stay (days)	1–5	37 (25.0)
	6–10	83 (56.08)
	≥11	28 (18.91)
Drug Prescribed/Patient	2–5	28 (18.91)
	6–9	67 (45.27)
	≥10	53 (35.81)
Proportion of pDDIs	Total number of patients	148 (100%)
	Patients with at least one pDDI	99 (66.89%)

It was observed that 99 prescriptions were found to have the potential for at least one or more DDIs with a prevalence rate of 66.89%, irrespective of the type of severity. The identified DDIs classified according to severity show that most of the interactions, 220 (40.07%) belong to the 'moderate' category, 155 (28.23%) were minor/non-significant, and 145 (26.41%) were classified 'minor.' A total of 29(5.28%) drug interactions were rated as a 'significant' severity category (Table 2).

Class of medications involved in causing drug interactions

The classification of pDDIs based on the Anatomical Therapeutic Classification (ATC) found a higher prevalence in the category cardiovascular system (28.8%) followed by anti-infective for systemic use (23.9%) and alimentary tract and metabolism (21.5%) (Figure 1).

Table 2. Types of drug combinations causing drug interactions identified in the study population.

Types of drug combinations with interacting pairs (n=116)	Level of Severity				Total number of DDIs (n=549) (%)	χ^2	P value
	Minor/non-significant (n=155) (%)	Minor (n=145) (%)	Moderate (n=220) (%)	Significant (n=29) (%)			
Non-antimicrobial agents *vs.* Antimicrobial agents (n=64)	115 (29.04)	95 (23.98)	167 (42.17)	19 (4.79)	396 (100)	37.52[†]	0.078
Non-antimicrobial agents *vs.* Non-antimicrobial agents (n=44)	38 (27.73)	47 (34.30)	44 (32.11)	08 (5.83)	137 (100)		
Antimicrobial agents *vs.* Antimicrobial agents (n=08)	02 (12.50)	03 (18.75)	09 (56.25)	02 (12.50)	16 (100)		

[†]Fisher's exact.
*p value <0.05 is statistically significant.

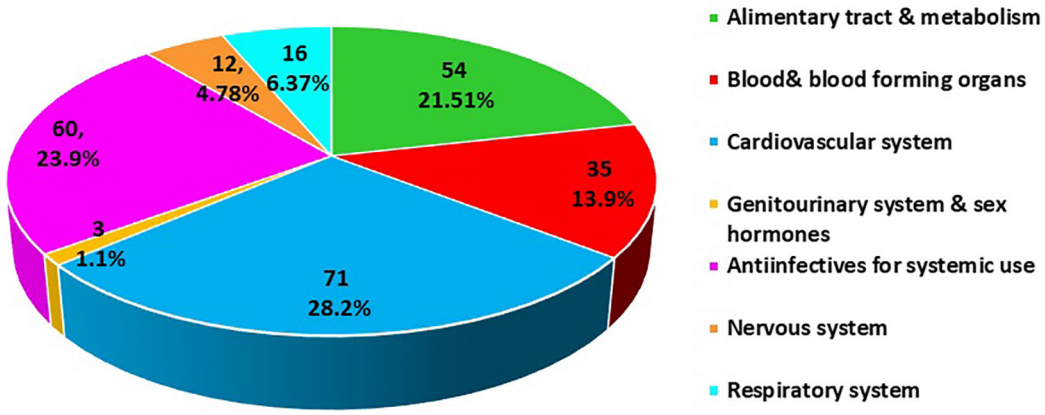

Figure 1. Anatomical Therapeutic Chemical (ATC) classification of drugs involved in potential drug-drug interactions (pDDIs).

The evaluation of the underlying mechanism that causes DDIs showed that 210 (38.25) interactions involve pharmacokinetic interactions, while 181 (32.96%) interactions were caused by 'others' or unknown mechanisms. The remaining 158 (28.77%) interactions were known to be produced by pharmacodynamic interactions.

The most frequently identified DDIs were the combination of atorvastatin with clopidogrel, bisoprolol, amlodipine, or pantoprazole; aspirin with insulin; clopidogrel enoxaparin and furosemide with valsartan; and lisinopril and bisoprolol. The antimicrobial drugs involved in pDDIs were combinations of ceftriaxone with enoxaparin and aspirin, levofloxacin with insulin, furosemide, and piperacillin/tazobactam with aspirin, metformin, and doxycycline (Table 3).

Factors associated with pDDIs in the study population

Analysis of the factors related to the appearance of pDDIs showed that there was a statistically significant association with age, comorbidities, length of hospital stay, and the number of drugs prescribed ($p<0.05$) (Table 4).

In the binary logistic regression analysis, the dependent variable was the presence or absence of pDDIs, and the predictor variables were age, comorbidities, hospital stay, and the number of drugs prescribed. Drug-drug interactions were significantly associated with comorbidities and the number of medications prescribed ($p<0.05$) (Table 5).

Table 3. Most common drug-drug interactions and their effect were identified among the study population.

Interaction	Drug combinations	Frequency	Effect	Level of concern	Source of recommendation
Significant	Aspirin – Enoxaparin	04	Both increase anticoagulation & Increase the risk of bleeding	04	pa
	Clopidogrel – Enoxaparin	08	Both increase anticoagulation & Increase the risk of bleeding	04	pa
	Bisoprolol – potassium chloride	04	Both increase serum potassium	04	a
	Valsartan – Sacubitril	04	Increased risk of renal impairment, hyperkalemia, hypotension,	04	a
	Metronidazole – levofloxacin	05	METRONIDAZOLE and LEVOFLOXACIN both increase QTc interval, Increased risk of long QT Syndrome, and possible Torsades de pointes	04	p
Moderate	Isoniazid – Rifampicin	05	Rifampin enhances the metabolism of isoniazid to hepatotoxic metabolites	03	a
	Levofloxacin – Furosemide	06	Increased risk of long QT Syndrome and possible Torsades de pointes	03	pa
	Bisoprolol – Aspirin	13	Both increase serum potassium	03	pa
	Amlodipine – Atorvastatin	16	Both levels probably increased – increased risk of arrhythmia, edema, myopathy, elevated liver function tests	03	pa
	Levodopa – piperacillin/tazobactam	04	Anticholinergics may enhance the therapeutic effects of LEVODOPA but may also exacerbate tardive dyskinesia. In high doses, anticholinergics may decrease the impact of LEVODOPA by delaying its GI absorption	03	a
Minor	Clopidogrel – Atorvastatin	14	Levels of Clopidogrel's active metabolite can be decreased	02	pa
	Insulin – levofloxacin	08	Insulin effects may be increased, and Quinolone antibiotic administration may result in hyper- or hypoglycemia	02	a
	Lisinopril – levodopa	03	LISINOPRIL effects may be increased Consider decreasing the dosage of an antihypertensive agent	02	a
	Aspirin – piperacillin/tazobactam	16	Both Piperacillin/Tazobactam (PIPERACILLIN) and ASPIRIN levels may be increased	02	a
	Clopidogrel – Amlodipine	05	Levels of CLOPIDOGREL's active metabolite can be decreased	02	pa
Minor/ non-significant	Bisoprolol/atorvastatin	17	Bisoprolol levels can be slightly increased, and Increased risk of bradycardia	01	pa
	Furosemide/piperacillin & tazobactam	06	Both decrease cholinergic effects/transmission Increased risk of anticholinergic syndrome (dilated pupils, vasodilation/ flushing, hyperthermia, dry skin)	01	p
	Metformin – furosemide	02	METFORMIN levels may be increased	01	a
	Memantine – metformin	01	Both drugs minimally increase the effects of the other drug involved in the mechanism	01	pa
	Clindamycin – piperacillin/tazobactam	02	CLINDAMYCIN and Piperacillin/Tazobactam (PIPERACILLIN) both decrease cholinergic effects/transmission Increased risk of anticholinergic syndrome (dilated pupils, vasodilation/ flushing, hyperthermia, dry skin, hallucinations/agitation, constipation/ urinary retention, tachycardia)	01	p

Level of concern: 01 - Minor or non-significant drug/drug interaction; 02 – Possible drug-drug interaction; 03 – Likely drug-drug interaction; 04 – Probable serious or life-threatening drug-drug interactions.
Source of Recommendation (SOR): p - predicted drug/drug interaction based on pharmacokinetic or pharmacodynamic principles; a - drug/drug interaction in literature; pa - predicted and recognized drug/drug interaction based on pharmacokinetic or pharmacodynamic principles.

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Table 4. Bivariate analysis of factors associated with potential drug-drug interactions among the study population.

Variables	Categories	Presence of DDIs [n(%)]	Absence of DDIs [n(%)]	χ^2	p-value
Sex	Male	56 (56.5)	21 (42.8)	2.46	0.116
	Female	43 (43.4)	28 (57.1)		
Age (in years)	≤20	5 (5.05)	5 (10.2)	13.82	**0.008***
	21–40	20 (20.2)	22 (44.8)		
	41–60	21 (21.2)	9 (18.3)		
	61–80	33 (33.3)	8 (16.3)		
	81 and above	20 (20.2)	5 (34.6)		
Comorbidities	Present	69 (69.6)	15 (30.6)	20.40	**<0.001****
	Absent	30 (30.3)	34 (69.3)		
Hospital stay (in days)	1–5	20 (20.2)	17 (34.6)	7.24	**0.027***
	6–10	55 (55.5)	28 (57.1)		
	≥11	24 (24.2)	04 (8.1)		
Number of drugs prescribed	2–5	9 (9.09)	19 (38.07)	23.03	**<0.001****
	6–9	45 (45.04)	22 (44.8)		
	≥10	45 (45.4)	8 (16.3)		

DDIs: drug-drug interactions.
*p<0.05 statistically significant.
**p<0.01 highly statistically significant.

Table 5. Multiple binary logistic regression analysis for factors associated with potential drug-drug interactions among the study population.

Variables	P value	Adjusted OR	Odds ratio (95% CI)
Age (in years)	0.158	0.545	0.234–1.267
Comorbidities	**0.019***	0.341	0.139–0.837
Hospital stay (in days)	0.338	1.721	0.567–5.223
Number of drugs prescribed	**0.025***	0.244	0.071–0.838

*p<0.05 statistically significant.

Discussion

Drug interactions contribute to undesirable health outcomes, compromise the clinical effectiveness of drug therapy, increase hospital visits, and prolong hospital stays.[21] The overall prevalence of pDDIs in our study was 67%, higher than the study by Hamdouk et al., who reported at least one pDDIs in 62.9%8% of the study sample.[22] Downward trends in prevalence were documented in earlier studies by Kuscu *et al.* (60%) and Rabba *et al.* (56%), respectively.[23,24]

This disparity in the prevalence of pDDIs may be attributed to the differences in the study setting, study population, prescribing pattern of medications, and types of pDDIs and tools used to screen drug interactions in the study. In the present study, the average was 3.70±4.58 drug interactions per prescription among hospitalized patients. Documented evidence indicates that drug interactions occur more predominantly in hospitalized patients than in outpatients, considering the severity of the disease, comorbidities, and prescription of multiple medications with frequent modifications during their stay.[25]

In the current study, aspirin, clopidogrel, statins, enoxaparin, furosemide, valsartan, and bisoprolol were prescribed to prevent and manage cardiovascular diseases. Documented evidence indicates that the use of these medications, either individually or in combination, is associated with various drug interactions, including increased bleeding, electrolyte

imbalances, renal failure, and hypotension.[23,25–27] However, prescribing these medications is sometimes unavoidable and therapeutically valuable as a lifesaving medication. Therefore, close monitoring for effective treatment and evaluation of the benefit-risk assessment of actual DDIs of prescribed drugs is warranted. At the same time, careful laboratory assessment of international normalized ratio, serum electrolytes, renal and liver function tests, signs and symptoms of bleeding, and blood pressure monitoring are vital during treatment.

Similarly, metformin, sitagliptin, insulin, tamsulosin, memantine, levodopa, pantoprazole, paracetamol, and supplements such as potassium chloride and calcium carbonate were some of the important medications prescribed for the various other medical conditions in our study. In addition, drugs such as penicillins, cephalosporins, fluoroquinolones, metronidazole, macrolides, doxycycline, linezolid, isoniazid, rifampicin, vancomycin, and amphotericin B were some of the important antimicrobial agents used in this study. Drugs that cause enzyme induction or inhibition, resulting in reduced metabolism or clinical effects and alteration of gastrointestinal absorption, are the most common mechanisms related to antimicrobial interactions.[28]

Cautious prescribing should be exercised when co-administering drugs with a narrow therapeutic index and drugs metabolized through cytochrome P450 isozymes that can develop clinically significant unpredictable drug interactions, particularly in patients with renal and hepatic impairment and the elderly population.[29–31] In the present study, the ATC class of medications involved in pDDIs showed a higher prevalence in the cardiovascular system (28.2%), followed by anti-infective for systemic use (23.9%). The increase in the prevalence of cardiovascular disease could be related to the use of complex medications for the long-term treatment of comorbidities and associated complications among the study populations. Our findings are consistent with those of Noor *et al*., Vazquez-Cornejo *et al.*, and Samardzic *et al*., who reported an increased prevalence of pDDIs in patients with cardiovascular disease.[25,26,30] Furthermore, an earlier study by Pavanello *et al.* in critical care patients showed that the most common drug class involved in pDDIs was anti-infective for systemic use, accounting for 45.8%, respectively.[28,32] The difference in study settings, varying profiles of study populations, disagreement in treatment guidelines and prescribing practice, and the use of different clinical decision support tools to analyze drug interactions may help explain the difference in the class of drugs involved in the onset of pDDIs.

In the present study, the severity level of most drug interactions was ‘moderate’ (40.0%) followed by ‘minor/non-significant’ (28.2%). Not all potential drug-drug interactions (pDDIs) are of equal severity, making the assessment of their severity crucial for recognizing their clinical significance and ensuring appropriate management. Only a small percentage (5.28%) of the identified drug interactions were found to be categorized as having a level of severity ‘significant,’ which requires close monitoring to avoid any adverse outcome of the pDDIs. It is suggested that a possible reason for the findings is that the risk factors and severity of potential drug-drug interactions (pDDIs) may be known to physicians, who might have tailored drug therapy to avoid or minimize these interactions.

These findings align with the results of the study by Noor *et al.* and Obeid *et al.*, who reported that most of the interactions were ‘moderate’ in severity.[26,33] Contrary to our findings, studies by Rabba *et al.* and Eneh *et al.* reported 66.4% and 52.7% of interactions with ‘major’ in severity level.[24,29] The difference in defining the classification and grading of severity between the resources could be a possible reason for the varying study results. Studies have observed that mechanism of action plays a significant role in DDIs, which requires management by either reducing the dose of one drug by 25% or 50%, changing the frequency of administration and dosage form, or avoiding such combination, replacing it with another medication.[25,34,35]

Our study showed that ‘pharmacokinetic interactions’ were the most common underlying mechanism that caused pDDIs compared to pharmacodynamic and other unknown mechanisms. Similar observations have been cited in the study by Tesfaye *et al*., who reported pharmacokinetic interactions as the most common mechanism involved in causing pDDIs compared with pharmacodynamic and other/unknown interactions.[36]

Studies have emphasized that patient characteristics such as age, comorbidities, number of medications prescribed, and hospital stay are risk factors for clinically significant pDDIs.[35,37,38] Age, comorbidities, length of hospital stay, and polypharmacy predispose patients to pDDIs. It is important to note that aging populations are at risk of developing multiple comorbid medical conditions that require frequent hospital visits and a prolonged stay prescribed with more complex therapeutic regimens.[39] Physiological changes related to age and variations in pharmacokinetics and pharmacodynamic parameters increase the risk and greater chance of developing pDDIs and adverse outcomes that reduce the efficacy of the treatment.[40] Pharmacists are essential in spotting possible drug-drug interactions (DDIs) and fixing them, which can greatly lower the chance of patient injury. Their participation in clinical decision-making and pharmaceutical therapy management is crucial for guaranteeing safe and efficient drug use, especially in intricate treatment plans.

Strengths
The strength of our study includes the prospective observational design, which allowed for real-time data collection and assessment of potential drug-drug interactions (pDDIs) in a clinical setting. Additionally, a comprehensive electronic health record system enhanced data accuracy and completeness. The study's focus on hospitalized patients with infectious diseases also provides valuable insights into medication management in this vulnerable population.

Limitations
Our study has a few limitations. First, only one database would limit the number of pDDIs and may not reflect all pDDIs. Using multiple database tools and comparisons may help define the results more explicitly. Second, the data for the present study were collected from the Wareed system and mainly focused on the theoretical pDDIs. Due to a lack of follow-up, they could not address the drug interactions and results from a clinical viewpoint. Third, the study only included patients with specific indications in the internal general medicine ward. Therefore, the findings cannot be extended or applied to other specialty wards, intensive care units, or outpatient settings. Finally, this study is an observational design, which did not include an intervention. The lack of an intervention may have limited the ability to directly impact patient outcomes and reduce the incidence of drug-drug interactions (DDIs). Implementing a targeted intervention, such as clinical decision support or tailored drug therapy, could have potentially improved patient outcomes and minimized the occurrence of harmful DDIs.

Conclusions
The present study identified a high frequency of pDDIs in hospitalized patients with infectious diseases. Antimicrobial agents and co-prescribed medications interacted; most of the interactions in our study had 'moderate' levels of severity. This study highlighted that advanced age, multiple comorbidities, and polypharmacy were independent risk factors for pDDIs. Knowledge about pDDIs and the regular use of professional drug information database support systems can help prescribers optimize drug therapy and enhance health outcomes. The study strongly recommends that regular review of patient drug therapy by a clinical pharmacist might avoid possible drug combinations that are likely to cause pDDIs and could ring a bell in improving the quality of patient-centered care.

Data availability
Underlying data
Figshare: ASSESSMENT OF POTENTIAL DRUG-DRUG INTERACTIONS IN HOSPITALIZED PATIENTS WITH INFECTIOUS DISEASES – AN EXPERIENCE FROM A SECONDARY CARE HOSPITAL. https://doi.org/10.6084/m9.figshare.24220714.v2.[41]

Acknowledgments
We want to thank the administration of Ibrahim Bin Hamad Obaidullah Hospital, Ras Al Khaimah, United Arab Emirates, for allowing us to conduct the study. The authors also thank the President of RAK Medical and Health Science University and the Dean of RAK College of Pharmacy for their encouragement and support.

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Open Peer Review

Current Peer Review Status: ✔ ✘ ✘ ✔

Version 4

Reviewer Report 03 January 2025

https://doi.org/10.5256/f1000research.175825.r355297

✔ **Abrar K Thabit**
Department of Pharmacy Practice, King Abdulaziz University, Jeddah, Saudi Arabia

I appreciate the authors' efforts in improving their manuscript. I approve the current version of the manuscript.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, clinical microbiology, clinical pharmacy, and academia.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 3

Reviewer Report 16 December 2024

https://doi.org/10.5256/f1000research.174389.r339909

✘ **Émilie Bortolussi-Courval**
[1] McGill University, Montreal, Québec, Canada
[2] McGill University, Montreal, Québec, Canada

Thank you for the opportunity to review this manuscript again. Below are my comments.

Please provide references for pharmacodynamic and pharmacokinetic definitions.

In the Results section, would the authors prefer using two decimal points or one decimal point? In the mean age (sd), authors present a mean with 2 decimal points with an sd of one decimal point. Please pick either one or two decimal points and harmonize this throughout the manuscript.

Authors did not mention the need to use IQR in the methods (i.e. mean/sd or median/IQR were reported as required). There is no way to know if the authors presented mean/sd when the median/IQR would have been more appropriate.

Can authors please provide a distinction between pDDIs and DDIs? Both are used throughout the manuscript making it difficult to understand the difference in the text.

My main comment is that authors make no visible mention of the fact that covariates were selected a priori, although they state having done so in the Version 2 Amendments paragraph. Again, this is a crucial item to include in the manuscript.

Authors did not correct an important typo that I had highlighted in the text:
What is "62.9%8%" ?

In Table 3, under the Sources of recommendation, authors did not provide a legend to indicate what the different letters mean ("a", "pa", etc.)

In Table 4, please harmonize one vs two decimal points.

What does the "number of drugs per prescription" mean?

Thank you for deleting Table 3. This new table is much clearer.

This text still requires substantial work.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Polypharmacy, deprescribing, medication safety, pharmacoepidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 22 Dec 2024

JAVEDH SHAREEF

Please provide references for pharmacodynamic and pharmacokinetic definitions
We have now included citations for all the definitions provided in the Mechanism of Interaction section. (Ref. 19)

In the Results section, would the authors prefer using two decimal points or one

decimal point? In the mean age (sd), authors present a mean with 2 decimal points with an sd of one decimal point. Please pick either one or two decimal points and harmonize this throughout the manuscript.
Regarding the decimal points used in the Results section, I appreciate your insightful observation. We both believe that it's critical to convey numerical facts consistently. We have standardised the use of decimal points throughout the manuscript in response to your advice. To maintain uniformity, we have specifically decided to utilise [two] decimal points for all mean values and standard deviations (SDs). We think that this method improves the presentation of our findings in terms of uniformity and clarity. We value your attention to this detail and have made the required changes across the manuscript.

Authors did not mention the need to use IQR in the methods (i.e. mean/sd or median/IQR were reported as required). There is no way to know if the authors presented mean/sd when the median/IQR would have been more appropriate
Acknowledge the reviewer's concern that the methodology section did not mention when to use mean/SD or median/IQR.
In our study, we used frequencies and percentages for categorical data and mean ± SD for continuous variables assuming a normal distribution. On the other hand, skewed or non-normally distributed data are better suited for the median and IQR. Since there was no discernible skewness in the data, we did not use them; however, you will examine the data once more to make sure that no variables should have been reported using median/IQR.

Can authors please provide a distinction between pDDIs and DDIs? Both are used throughout the manuscript making it difficult to understand the difference in the text..
DDIs typically refer to confirmed or clinically observed drug-drug interactions whereas pDDIs refer to interactions that are identified based on theoretical or database-generated information, but have not yet been confirmed clinically in the study population. Thank you for pointing out the potential confusion between pDDIs and DDIs in the manuscript. Given that our study is observational and uses database tools to identify drug-drug interactions, the correct terminology in our context should be pDDIs (potential drug-drug interactions) rather than DDIs (drug-drug interactions).

My main comment is that authors make no visible mention of the fact that covariates were selected a priori, although they state having done so in the Version 2 Amendments paragraph. Again, this is a crucial item to include in the manuscript..
Thank you for your insightful comment. We acknowledge that the manuscript does not clearly mention that covariates were selected a priori, which is an important methodological detail. This oversight will be addressed in the revised manuscript.

To clarify, covariates for our analysis were selected a priori, based on the relevant literature, clinical relevance, and prior studies related to drug-drug interactions (DDIs/pDDIs). We intended to ensure that our analysis would be driven by established factors known to influence drug interactions, rather than performing post hoc selection. We agree that this detail is crucial to include in the manuscript for full transparency and methodological clarity.

Authors did not correct an important typo that I had highlighted in the text:

What is "62.9%8%" ?
I appreciate you pointing up the manuscript's typo. The error where "62.9%8%" was mentioned has been found and fixed. "62.9%" is now the updated correct value. We value your attention to detail and really regret this oversight.

In Table 3, under the Sources of recommendation, authors did not provide a legend to indicate what the different letters mean ("a", "pa", etc.)?
In response, we have added a footnote to **Table 3** to clarify the **Level of Concern** and **Source of Recommendation (SOR)** for each drug-drug interaction (DDI). The footnote includes the following information:

- **Level of Concern**:
  - 01 – Minor or non-significant drug/drug interaction
  - 02 – Possible drug-drug interaction
  - 03 – Likely drug-drug interaction
  - 04 – Probable serious or life-threatening drug/drug interaction
- **Source of Recommendation (SOR)**:
  - p – Predicted drug/drug interaction based on pharmacokinetic or pharmacodynamic principles
  - a – Drug/drug interaction in literature
  - pa – Predicted and recognized drug/drug interaction based on pharmacokinetic or pharmacodynamic principles

This footnote should help clarify how the DDIs are categorized and the source of their recommendation, addressing the point raised.

In Table 4, please harmonize one vs two decimal points.?
Thank you for your helpful suggestion. We have reviewed and harmonized the decimal points in Table 4, ensuring consistency throughout the table by using [two] decimal points. We believe this improves the clarity and presentation of the data.

What does the "number of drugs per prescription" mean?
The "number of drugs per prescription" refers to the total count of different medications prescribed in a single prescription to a patient during their hospital stay.

Thank you for deleting Table 3. This new table is much clearer.
I appreciate your compliments. We are happy that the updated table is more useful and understandable. Since it has enabled us to present the data in a more succinct and comprehensible manner, we appreciate your idea to remove Table 3.

Competing Interests: No competing interests were disclosed.

Reviewer Report 05 December 2024

https://doi.org/10.5256/f1000research.174389.r343772

?

Abrar K Thabit
[1] Department of Pharmacy Practice, King Abdulaziz University, Jeddah, Saudi Arabia
[2] Department of Pharmacy Practice, King Abdulaziz University, Jeddah, Saudi Arabia

This is a good study that evaluated potential DDIs among patients hospitalized with infectious diseases. It provides some valuable insights that could be overlooked by clinicians. However, several issues need to be addressed.

Abstract:
1. In the methods, remove the text on ethical committee approval and statistical analysis. Instead, mention how you classified these DDIs based on severity since you commented on that in the conclusion.
2. Results: Also, briefly mention something about the severity level of the most common DDIs.

Introduction:
3. Correct "Infectious infections" to Infectious diseases"

Methods:
4. Assessment of drug-drug interactions: Please cite the reference based on which you classified the DDIs based on severity. Also, please remove this statement and move it to the data analysis section: "The collected data were scrutinized and checked for completeness, clarity, and legibility before being entered into a Microsoft Excel (RRID: SCR_016137) spreadsheet and were later analyzed using IBM SPSS Statistics (RRID: SCR_016479) version 27. (IBM Corp., Armonk, NY, USA)."
5. Severity level of the drug interaction: This section should be combined with the previous one as they're strongly related.
6. Mechanism of interaction: Again, cite the references of all the definitions.
7. Data analysis: mean and standard deviation are used to describe continuous data and not categorical data. Please correct.

Results:
8. Table 1: Remove the "SI No" column.
9. Class of medications involved in causing drug interactions: The following statement should be moved to the methods with a citation of the website: "The analysis of the class of medications involved in the onset of pDDIs carried out using the Anatomical Therapeutic Chemical (ATC) classification system derived by the World Health Organization."
10. Figure 1: The figure appears blurry. Please improve the quality of the figure.
11. Table 5: Replace "Exp(B)" with "Adjusted OR". Also, the last column should be titled "95% confidence interval" only. I also suggest removing the following columns as they don't offer very useful information beside the adjusted OR, 95% CI, and P value: The beta coefficient of predictor variables, Standard error, and Wald. Also, remove the constant row.
12. In the methods, you mentioned pharmacokinetic and pharmacodynamic interactions. However, I don't see any classification of the reported DDIs based on these definitions. I suggest adding a column to Table 3 classifying each interaction into one of these two categories.

Discussion:
13. This statement should be rephrased for clarity: "The current study prescribed aspirin, ..."
14. Rephrase this statement and make it in a passive tense: "The author suggests that ..."

Limitations:
15. I think among the limitations is the lack of intervention given the observational study design. Making an intervention would have improved the patients outcomes and reduced the incidence of DDIs.

Conclusion:
16. Replace "higher" with "high"
17. I suggest including a statement emphasizing the critical role of pharmacists on spotting these DDIs and potentially reducing patient harm by resolving them as possible.

General comment:
18. I didn't see any interaction between fluoroquinolones and minerals, such as iron and calcium which are commonly given to hospitalized patients. I also wondered the lack of interactions between fluoroquinolones and macrolides with QT-prolonging agents, such as antiarrhythmics and antidepressants. Were these not reported at all?

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, clinical microbiology, clinical pharmacy, and academia.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Dec 2024

JAVEDH SHAREEF

Abstract:
In the methods, remove the text on ethical committee approval and statistical analysis. Instead, mention how you classified these DDIs based on severity since you commented on that in the conclusion.
Author Response: We deleted the elements about the statistical analysis and ethical committee approval from the abstract. In addition, we updated the methods section to illustrate how the DDIs were categorized according to their severity level. In particular, we identified potential DDIs (pDDIs) using the PEPID database and then classified them based on severity levels.

Results: Also, briefly mention something about the severity level of the most common DDIs.
Author Response: We have added a brief note about the severity levels of the most prevalent DDIs in the study to the Results section. To contextualize the clinical significance of these findings, we specifically emphasized the severity level distribution among the most commonly detected interactions.

Introduction:
Correct "Infectious infections" to Infectious diseases"
Author Response: As suggested, we have changed the term "Infectious infections" to "Infectious diseases" in the Introduction section.

Methods:
Assessment of drug-drug interactions: Please cite the reference based on which you classified the DDIs based on severity. Also, please remove this statement and move it to the data analysis section: "The collected data were scrutinized and checked for completeness, clarity, and legibility before being entered into a Microsoft Excel (RRID: SCR_016137) spreadsheet and were later analyzed using IBM SPSS Statistics (RRID: SCR_016479) version 27. (IBM Corp., Armonk, NY, USA)."
Author Response: We have updated the Methods section with the relevant reference for the severity-based DDI classification.
Following your recommendation, we have repositioned the statement about the data entry and analysis processes to the Data Analysis section for improved organization and clarity.

Severity level of the drug interaction: This section should be combined with the previous one as they're strongly related.
Author Response: We have merged the two sections to enhance the organization and readability of the manuscript, as suggested.

Mechanism of interaction: Again, cite the references of all the definitions.
Author Response: We have now included citations for all the definitions provided in the **Mechanism of Interaction** section.

Data analysis: mean and standard deviation describe continuous data, not categorical data. Please correct

Author Response: We have updated the Data Analysis section to ensure that frequencies, percentages, or proportions are used appropriately when describing categorical data.

Results:
Table 1: Remove the "SI No" column.
Author Response: As per your recommendation, we have removed the "SI No" column from Table 1. The table has been updated to reflect this change.

Class of medications involved in causing drug interactions: The following statement should be moved to the methods with a citation of the website: "The analysis of the class of medications involved in the onset of pDDIs carried out using the Anatomical Therapeutic Chemical (ATC) classification system derived by the World Health Organization."
Author Response: We have relocated the statement about analyzing drug classes using the Anatomical Therapeutic Chemical (ATC) classification system to the Methods section and included references to the World Health Organization's (WHO) ATC classification system.

Figure 1: The figure appears blurry. Please improve the quality of the figure
Author Response: We have improved the quality of the figure and replaced the original with a higher-resolution version to ensure it is clear and legible.

Table 5: Replace "Exp(B)" with "Adjusted OR". Also, the last column should be titled "95% confidence interval" only. I also suggest removing the following columns as they don't offer useful information besides the adjusted OR, 95% CI, and P value: The beta coefficient of predictor variables, Standard error, and Wald. Also, remove the constant row.
Author Response: As you recommended, we have replaced "Exp(B)" with "Adjusted OR. " The last column has been renamed "95% Confidence Interval" to clarify the information presented. I have removed the columns for the beta coefficient of predictor variables, standard error, and Wald statistic, as these do not contribute additional useful information beyond the adjusted OR, 95% CI, and p-value. The "constant row" has also been removed from the table.

In the methods, you mentioned pharmacokinetic and pharmacodynamic interactions. However, based on these definitions, I don't see any classification of the reported DDIs. I suggest adding a column to Table 3 to classify each interaction into one of these two categories.
Author Response: In response, we have added a footnote to **Table 3** to clarify the **Level of Concern** and **Source of Recommendation (SOR)** for each drug-drug interaction (DDI). The footnote includes the following information:

- **Level of Concern**:
  - 01 – Minor or non-significant drug/drug interaction
  - 02 – Possible drug-drug interaction
  - 03 – Likely drug-drug interaction
  - 04 – Probable serious or life-threatening drug/drug interaction
- **Source of Recommendation (SOR)**:
  - p – Predicted drug/drug interaction based on pharmacokinetic or pharmacodynamic principles

- a – Drug/drug interaction in literature
- pa – Predicted and recognized drug/drug interaction based on pharmacokinetic or pharmacodynamic principles

This footnote should help clarify how the DDIs are categorized and the source of their recommendation, addressing the point raised.

This statement should be clarified: "The current study prescribed aspirin, ..."
Author Response: We have clarified the language by rephrasing it in response. The new phrase follows: "In the current study, aspirin, clopidogrel, statins, enoxaparin, furosemide, valsartan, and bisoprolol were prescribed for the prevention and management of cardiovascular diseases."

Rephrase this statement and make it in a passive tense: "The author suggests that ..."
Author Response: We have rephrased the sentence in the passive voice as follows:
"It is suggested that a possible reason for the findings is that physicians may be aware of the risk factors and severity of potential drug-drug interactions (pDDIs) and might have tailored drug therapy to avoid or minimize these interactions."

Limitations:
15. I think among the limitations is the lack of intervention given the observational study design. Intervening would have improved the patient's outcomes and reduced the incidence of DDIs.
Author Response: I concur that the study's observational design restricts the application of an intervention that might enhance patient outcomes and lower the frequency of drug-drug interactions (DDIs). We have added the following to the drawbacks section per your suggestion: "This study's observational design, which lacked an intervention, is one of its drawbacks.

Conclusion:
Replace "higher" with "high"
Author Response: We have replaced "higher" with "high" in the **Conclusion** section, as recommended, to improve the clarity and accuracy of the statement

I suggest including a statement emphasizing the critical role of pharmacists in spotting these DDIs and potentially reducing patient harm by resolving them as soon as possible.
Author Response: We have added the following statement to the **Discussion** section:
"Pharmacists are essential in spotting possible drug-drug interactions (DDIs) and fixing them, which can greatly lower the chance of patient injury. Their participation in clinical decision-making and pharmaceutical therapy management is crucial for guaranteeing safe and efficient drug use, especially in intricate treatment plans.

General comment:
I didn't see any interaction between fluoroquinolones and minerals, such as iron and calcium, commonly given to hospitalized patients. I also wondered about the lack of interactions between fluoroquinolones and macrolides with QT-prolonging agents, such as antiarrhythmics and antidepressants. Were these not reported at all?

Author Response: In our study, we evaluated potential drug-drug interactions (pDDIs) using the PEPID database. The database may report different interactions and may not always consistently identify the same interactions. The severity levels of interactions (ranging from mild to severe) might also differ between databases, and some interactions found in one database might not be included in another.

Even though patients in our study were prescribed macrolides, fluoroquinolones, and QT-prolonging medications such as antidepressants and antiarrhythmics, the PEPID database did not find any interactions between these medications. The criteria for evaluating possible interactions or the database's particular constraints could cause this. We acknowledge that the specific database employed may impact the identification of pDDIs, and this variability should be taken into account when interpreting the findings.

Competing Interests: No competing interests were disclosed.

Version 2

Reviewer Report 22 October 2024

https://doi.org/10.5256/f1000research.169291.r329857

Émilie Bortolussi-Courval
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Thank you for the opportunity to review this manuscript. This prospective observational study analyzed potential drug-drug interactions (pDDIs) among hospitalized adults with an infectious disease.

Based on my assessment, I do not believe authors sufficiently cited literature. In the introduction, there should be citations for the definition of a DDI. When authors mention "studies have reported that age, polypharmacy (...)", they do not cite any study to support these sttements. In the methodology, I was expecting citations for the European Medicines Agency Guidelines. I was disappointed to see that there were no guidelines followed for reporting the findings of this study, such as the STROBE guidelines.

Methods
When, during the course of the study, were the covariates selected? Was selection done a priori or posthoc? This is a very important clarification to make.

Definitions would have been required for pharmacokinetic and pharmacodynamic interactions.

Were median/IQR ever necessary to use in this study, in the case of demographic data that was not normally distributed?

Women may have more pDDIs because of a baseline longer QT interval; would it be possible to stratify outcomes according to sex?

Results
Were there significantly more patients in a particular age group versus another?

I believe the prevalence of pDDIs should be described in the Results section of the manuscript. This is an important finding that the reader should appreciate quickly.

What does "the average number of drugs per prescription was 8.35±3.19 medications" mean? I'm not sure I understand.

Table 3: I do not understand the utility of this table. It appears as though several non-antimicrobial drugs are listed alone. Would it be possible to only use Figure 1? I believe it is more telling of the classes of drugs that were involved rather than the list of agents involved. The other issues I have with Table 3 are that i) there is no indication of the frequency of involvement of each medication in an interaction, and ii) Amphotericin B should belong in the antimicrobial category, not the non-antimicrobial category.

In the discussion, "cautious prescribing should be exercised when co-administering drugs with a narrow therapeutic index (...)", I was expecting citations for this. Was this from UpToDate? If so, it would require a citation.

"A possible reason could be that physicians are aware of the risk factors and severity of pDDIs" : has this been previously documented in the literature? If so, a citation would be needed here.

"It is important to note that aging populations are at risk of developing multiple comorbid medical conditions that require frequent hospital visits and a prolonged stay prescribed with more complex therapeutic regimens". Is there a citation for this?

Would the authors be able to provide the proportion of patients with a pDDI in the Results section of Table 1?

There are several typos within the discussion that need to be fixed.

What does "62.9%8% of the study sample" mean?
Please fix this sentence: "All pDDIs. are not identical in severity and evaluating their severity l is very important to recognize their clinical significance and proper management."

What are the strengths of this study? I was expecting to see this in the discussion.

I do not see the relevance of the following sentence with the rest of the paragraph: "A review of

the published evidence suggests that fluoroquinolones and macrolides are associated with QT prolongation and may cause life-threatening arrhythmias." I would consider removing it.

Given the several oversights that I have seen within the manuscript (omission of citation of studies despite referencing of "several studies", adding an antimicrobial agent in a under "non antimicrobial agent" column by mistake, several typos in the discussion) that make the interpretation of the study findings difficult, I am not able to accept this manuscript at this time. This study has the potential to be an important addition to the literature in the field, but there are several issues with the methodology and results of the manuscript that require clarification.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Polypharmacy, deprescribing, medication safety, pharmacoepidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 03 Nov 2024

JAVEDH SHAREEF

In the introduction, there should be citations for the definition of a DDI.
Thank you for your valuable feedback regarding the definition of drug-drug interactions (DDIs) in the introduction. In the updated manuscript, I have provided proper citations for the concept of a DDI, specifying the sources in the reference list (**Ref. 01**) for clarity.

When authors mention "studies have reported that age, polypharmacy (...)", they do not cite any study to support these statements.

I have reviewed the relevant literature and included primary studies as citations in the revised manuscript to substantiate these assertions (Ref. 6,7).

In the methodology, I was expecting citations for the European Medicines Agency Guidelines.
I have added citations for the European Medicines Agency Guidelines in the revised manuscript to support our methodology accurately (Ref. 18).

When, during the course of the study, were the covariates selected? Was selection done a priori or posthoc? This is a very important clarification to make.
Before data collection and analysis, the covariates were chosen based on current literature and the clinical significance of potential drug-drug interactions (pDDIs).

Definitions would have been required for pharmacokinetic and pharmacodynamic interactions.
The updated manuscript has included precise definitions of pharmacokinetic and pharmacodynamic interactions.

Were median/IQR ever necessary to use in this study, in the case of demographic data that was not normally distributed?
We appreciate your interest in presenting demographic data using the median and interquartile range (IQR).
We appreciate your interest in presenting demographic data using the median and interquartile range (IQR). Normality tests indicated that age and length of hospital stay were roughly normally distributed, so we presented these variables' mean and standard deviation (SD).
In future studies, we will consider using the median and IQR where data is skewed.

Women may have more pDDIs because of a baseline longer QT interval; would it be possible to stratify outcomes according to sex?
While our current analysis did not include sex-specific stratification, we recognize that stratifying outcomes by sex could provide valuable insights. Future studies will consider this approach to understand pDDIs across demographic groups better.

Were there significantly more patients in a particular age group versus another?
Our analysis found that most patients fell within the 21–40 and 61–80 age ranges, with significant associations ($p<0.05$) between these age categories and pDDIs. In future studies, we will clarify these findings and consider a further breakdown of age-related data to enhance our understanding of age as a factor in pDDIs.

I believe the prevalence of pDDIs should be described in the Results section of the manuscript. This is an important finding that the reader should appreciate quickly.
We have modified the Results section to include the prevalence rate of pDDIs among our study population. Highlighting this important finding can enhance the clarity and impact of our manuscript.

What does "the average number of drugs per prescription was 8.35±3.19 medications"

mean? I'm not sure I understand.
The statement "the average number of drugs per prescription was 8.35±3.19 medications" means that, on average, each patient was prescribed about 8.35 medications, with ±3.19 indicating the standard deviation.

Table 3: I do not understand the utility of this table. It appears as though several non-antimicrobial drugs are listed alone. Would it be possible to only use Figure 1? I believe it is more telling of the classes of drugs that were involved rather than the list of agents involved. The other issues I have with Table 3 are that i) there is no indication of the frequency of involvement of each medication in an interaction, and ii) Amphotericin B should belong in the antimicrobial category, not the non-antimicrobial category.
Thank you for your feedback regarding Table 3. Utility of Table 3: To enhance clarity, I have removed Table 3 and will rely solely on Figure 1 for a streamlined presentation of drug classes involved in pDDIs. Amphotericin B has been reclassified as an antimicrobial agent.

In the discussion, "cautious prescribing should be exercised when co-administering drugs with a narrow therapeutic index (...)", I was expecting citations for this. Was this from UpToDate? If so, it would require a citation.
The revised manuscript has included citations to support this claim (Ref. 27-29). This information was obtained from the previous similar studies, I have properly cited it in the revised text.

A possible reason could be that physicians are aware of the risk factors and severity of pDDIs": has this been previously documented in the literature? If so, a citation would be needed here.
This observation was an author's assumption based on our study's results rather than documented in previous studies. I have revised the text to clarify that this is an author's hypothesis rather than a literature-supported statement.

"**It is important to note that aging populations are at risk of developing multiple comorbid medical conditions that require frequent hospital visits and a prolonged stay prescribed with more complex therapeutic regimens". Is there a citation for this?**
I have included relevant studies as citations supporting this claim in the revised manuscript (**Ref. 37).**

Would the authors be able to provide the proportion of patients with a pDDI in the Results section of Table 1?
Thank you for your suggestion. I calculated and included the proportion of patients with pDDIs in the revised manuscript in Table 1.

Please fix this sentence: "All pDDIs. are not identical in severity and evaluating their severity l is very important to recognize their clinical significance and proper management."
Thank you for your feedback. The sentence has been revised in the manuscript for clarity.

I do not see the relevance of the following sentence with the rest of the paragraph: "A

review of the published evidence suggests that fluoroquinolones and macrolides are associated with QT prolongation and may cause life-threatening arrhythmias." I would consider removing it.
Thank you for your comment. The sentence about fluoroquinolones and macrolides has been removed to improve paragraph coherence.

What are the strengths of this study? I was expecting to see this in the discussion.
I have added a detailed discussion of the study's strengths in the revised manuscript to highlight our contributions to pDDI research.

Competing Interests: No competing interests were disclosed.

Reviewer Report 29 August 2024

https://doi.org/10.5256/f1000research.169291.r312034

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The suggested changes and corrections are done in the revised version.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
No

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infectious diseases, diabetes care, hypertension therapy, liver diseases, serum enzyme study

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 28 June 2024

https://doi.org/10.5256/f1000research.156820.r289750

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Assessment of potential drug-drug interactions in hospitalized patients with infectious diseases: an experience from a secondary care hospital
The authors aimed to assess potential drug-drug interactions (pDDIs) among hospitalized patients with infectious diseases in a secondary care hospital.

1. There is an inconsistency in the mention of “pDDIs”, “DDI”, drug–drug interactions and “drug interaction” across the manuscript.
2. There is a significant flaw in the study objectives, design and results. The study objective states that “Therefore, the present study was carried out to assess pDDIs among hospitalized patients with infectious diseases receiving antimicrobial agents in a secondary care hospital.” However, the study also reports on the pDDIs between 2 non-antimicrobial agents. Many pDDIs reported in Table 4 are between 2 non-antimicrobial agents, which may not justify the title and objectives.
3. There is a fundamental flaw in this study. Table 1 reports that tuberculosis is present in 1 patient as a comorbidity among 148 hospitalized patients studied. Whereas Table 4 shows that the frequency of Isoniazid-Rifampicin pDDI is 5, which cannot be possible. Further, isoniazid is administered along with rifampicin, and other antitubercular agents such as pyrazinamide and ethambutol as a combined fixed dose formulation to TB patients.

4. To justify the title and the objectives, the authors may focus on the identification of the pDDIs between the antimicrobial agents and between antimicrobial agents and other drug categories. Identify the frequency of the top interacting antimicrobial agents and their mechanism and classify based on the infection categories.
5. Table 1 has listed on the different comorbidities in the 148 hospitalized patients. What are the comorbidities, where a higher frequency of pDDIs between antimicrobial agents and other drug categories were observed?
6. Since this is a scientific manuscript, the detailed elaboration on the need for obtaining necessary ethics committee approval from the hospital in a paragraph is not required as mentioned in the study setting.
7. Most of the statements mentioned in the patient demographics are a repetition of the Table 1. There is no need for repeating the results and table.
8. Also, many result statements are repeated in the discussion section.
9. The study aimed to assess the potential drug-drug interaction among hospitalized patients with infectious diseases using only a single electronic physician information database (PEPID) interaction tool (mentioned in limitation).
10. In the Table 5, for the column- presence and absence of DDI, n and % is mentioned in column title, but only n is present in the results. Also is it “Number of drugs prescribed” instead of “No drugs prescribed”?.
11. The current manuscript requires extensive editing of English language.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Drug-drug interactions, clinical pharmacy, precision medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 16 May 2024

https://doi.org/10.5256/f1000research.156820.r272895

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The authors have studied 148 patient case records to assess the potential drug-drug interactions in hospitalized patients with infectious diseases giving more emphasis on comorbidity cases.

The manuscript addresses the potential drug-drug interactions in hospitalized patients with infectious diseases. Since there are many studies investigating this theme, it is not clear how this research adds to the current field.

A statement of confirmation that the study conforms to recognised ethical standards should be included (for example: Declaration of Helsinki; US Federal Policy for the Protection of Human Subjects; European Medicines Agency Guidelines for Good Clinical Practice).

The title of article states that ''Assessment of potential drug-drug interactions in hospitalized patients with **infectious diseases**''.....but the result states majority of drug interaction with non-antimicrobial combinations, ''396 drug interactions 64 non-antimicrobial combinations''. When the work was focused on patients with infectious diseases, majority of cases should have been included DDIs with non-antimicrobial and antimicrobial combinations, or antimicrobial combinations.

Is the study design appropriate and is the work technically sound?

The method described is not detailed enough to warrant possibility of replication by the readers. Details of the experimental setting, timeline, research questions, and references of the methods/scales have to be better explained.
Also no description of infectious diseases is provided whereas all comorbidities are elaborately described.
The method of identification of drug-drug interaction results is not described.

The text needs editing and language review, eg Polypharmacy is common among hospitalized patients with **infectious infections** .....

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infectious diseases, diabetes care, hypertension therapy, liver diseases, serum enzyme study

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 16 Jul 2024

JAVEDH SHAREEF

COMPLIANCE TO REVIEWER COMMENTS
Manuscript title: ASSESSMENT OF POTENTIAL DRUG-DRUG INTERACTIONS IN HOSPITALIZED PATIENTS WITH INFECTIOUS DISEASES – AN EXPERIENCE FROM A SECONDARY CARE HOSPITAL

Authors: JAVEDH SHAREEF, Sathvik Belagodu Sridhar1, Abu Nawa Ahmad Ismail1, Padma G.M. Rao1, Rashid Ain Ur2
Reviewer – 1
Rina Das, MM College of Pharmacy, Maharishi Markandeshwar University, Ambala, Haryana, India
Sl No
Reviewer (comments)
Corrections Made
Page No.

1. The authors have studied 148 patient case records to assess the potential drug-drug interactions in hospitalized patients with infectious diseases giving more emphasis on comorbidity cases.
The manuscript addresses the potential drug-drug interactions in hospitalized patients with

infectious diseases. Since there are many studies investigating this theme, it is not clear how this research adds to the current field.
Response: Thank you for your valuable feedback. Our investigation of pDDIs among hospitalized patients with infectious illnesses in the UAE adds a novel perspective to the current literature. While there are several global studies on this issue, our research is relevant to the UAE healthcare system, considering local prescription patterns, common infectious illnesses, and distinct patient demographics. By evaluating 148 patient case records, focusing on comorbidities, we present insights specific to this geographical situation. This localized approach broadens our understanding of medication safety and management measures, particularly in the UAE, with practical implications for enhancing patient care and outcomes in our healthcare system.
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2. A statement of confirmation that the study conforms to recognised ethical standards should be included (for example: Declaration of Helsinki; US Federal Policy for the Protection of Human Subjects; European Medicines Agency Guidelines for Good Clinical Practice).
Response: Thank you for your feedback. We confirm that our study "Assessment of potential drug-drug interactions in hospitalized patients with infectious diseases: an experience from a secondary care hospital" adheres to recognized ethical standards. This study was performed per the principles outlined in the Declaration of Helsinki, the US Federal Policy for the Protection of Human Subjects (Common Rule), and the European Medicines Agency Guidelines for Good Clinical Practice.
04

3. The title of article states that ''Assessment of potential drug-drug interactions in hospitalized patients with infectious diseases''.....but the result states majority of drug interaction with non-antimicrobial combinations, ''396 drug interactions 64 non-antimicrobial combinations''. When the work was focused on patients with infectious diseases, majority of cases should have been included DDIs with non-antimicrobial and antimicrobial combinations, or antimicrobial combinations.
Response: Thank you for your insightful observation. Our study aimed to investigate pDDIs in hospitalized patients with infectious diseases and also looked at interactions with antimicrobial and non-antimicrobial medications. This divergence from the stated aims could be clarified by emphasizing the comprehensive nature of our investigation into pDDIs, encompassing interactions across all medication classes administered to the patient group. This approach aimed to thoroughly assess potential interactions that could impact clinical management in secondary care settings.
The primary aim of our study was to investigate pDDIs involving antimicrobial drugs, which are important in treating infectious disorders. However, throughout the process, we discovered substantial interactions with non-antimicrobial drugs, which might have an equivalent impact on patient outcomes. Including these data gives a more comprehensive understanding of the drug management problems that hospitalized patients experience. Our work provides a stronger platform for improving clinical procedures and guaranteeing patient safety by recognizing and managing antimicrobial and non-antimicrobial pDDIs.

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4. The method described is not detailed enough to warrant possibility of replication by the readers. Details of the experimental setting, timeline, research questions, and references of the methods/scales have to be better explained.
Also no description of infectious diseases is provided whereas all comorbidities are elaborately described.
The method of identification of drug-drug interaction results is not described.
Response: The methodology section has been revised to include details about the study setting, ethical approval, inclusion/exclusion criteria, study duration, reference to the drug interaction tools used, and method of assessing drug-drug interactions.
A description of infectious diseases is provided in the first paragraph of the introduction section.
4-6 & 03

5. The text needs editing and language review, e.g., Polypharmacy is common among hospitalized patients with infectious infections .....
Response: All the grammatical and construction errors have been rectified with the help of an English language expert and incorporated in the updated version of the manuscript.
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6. Is the work clearly and accurately presented and does it cite the current literature?

Yes
Thank you!
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Competing Interests: No competing interests were disclosed.