Evaluation of the Potential Drug-Drug Interactions among Hospitalized Patients with COVID-19: A Cross-Sectional Study

COVID-19 Tanısı ile Hastanede Yatan Hastalar Arasında Olası İlaç-İlaç Etkileşimlerinin Değerlendirilmesi: Kesitsel Bir Çalışma

Emine Nur Özdamar[1], Berrak Sahtiyancı[2]

[1] Department of Medical Pharmacology, Faculty of Medicine, Yeditepe University, Istanbul, Türkiye
[2] Department of Internal Medicine, Istanbul Bahçelievler Public Hospital, Istanbul, Türkiye

ABSTRACT

Objective: COVID-19 related drugs and concomitantly used drugs of the patients for their co-morbid diseases may enhance the risk for having potential drug-drug interactions (pDDIs) during hospitalization. The aim of the present study was to identify the frequency and severity of pDDIs between the COVID-19 treatment options and concomitantly used drugs at COVID-19 inpatient clinics of a public hospital.
Methods: A total of 321 files of the patients with COVID-19 who were hospitalized at inpatient clinics of a public hospital were assessed retrospectively. The frequency, risk category and severity of the pDDIs were assessed according to the Lexi-comp® online drug interaction database.
Results: A vast majority of the patients (99.1%) had at least one pDDI with a maximum of 25 pDDIs. The most commonly detected pDDIs were between Favipiravir and Paracetamol (B risk category), (24.4%), followed by the pDDIs between Enoxaparin-Acetylsalicylic acid (D risk category), (10.1%) drug pairs. Hyper-polypharmacy (≥10 drugs) was significantly and positively associated with male gender (p=0.023), adult age group (p=0.002) and co-morbid diabetes mellitus (p<0.001) and essential hypertension (p<0.001). The presence of moderate to major pDDIs was significantly and positively associated with male gender (p=0.012) and adult age group (p=0.019).
Conclusion: The present study revealed that the frequency of pDDIs among hospitalized patients with COVID-19 are quite high. Although the severity of pDDIs at COVID-19 inpatient clinics in general, are moderate and preventable, physicians should pay a particular attention regarding the pDDIs which may have life-threatening consequences such as the risk of bleeding.

Keywords: Drug interactions, Covid-19, Hospitalization, Favipiravir, Acetylsalicylic acid, Paracetamol

Received: 01.03.2022 **Accepted:** 08.10.2022

ÖZET

Amaç: COVID-19 ile ilişkili ilaçlar ve hastaların eşlik eden hastalıkları nedeniyle birlikte kullandıkları ilaçlar, hastanede yatış sırasında olası ilaç-ilaç etkileşimleri riskini artırabilir. Bu çalışmanın amacı, bir devlet hastanesinin COVID-19 yataklı kliniklerinde COVID-19 tedavi seçenekleri ile eş zamanlı kullanılan ilaçlar arasındaki olası ilaç-ilaç etkileşimlerinin sıklığını ve şiddetini belirlemektir.
Yöntem: Bir devlet hastanesinin yataklı kliniklerinde yatan COVID-19 hastalarına ait toplam 321 dosya retrospektif olarak incelendi. Olası ilaç-ilaç etkileşimlerinin sıklığı, risk kategorisi ve şiddeti, Lexi-comp® çevrimiçi ilaç etkileşimi veri tabanına göre değerlendirildi.
Bulgular: Hastaların büyük çoğunluğunda (%99,1) en az bir ve maksimum 25 olası ilaç-ilaç etkileşimi vardı. En sık tespit edilen olası ilaç-ilaç etkileşimleri Favipiravir ve Parasetamol (B risk kategorisi) (%24,4) arasında olup, bunu Enoksaparin-Asetilsalisilik asit (D risk kategorisi) (%10,1) ilaç çiftleri arasındaki olası ilaç-ilaç etkileşimleri izlemektedir. Hiperpolifarmasi (≥10 ilaç) erkek cinsiyet (p=0,023), yetişkin yaş grubu (p=0,002) ve eşlik eden diabetes mellitus (p<0,001) ve esansiyel hipertansiyon (p<0,001) ile anlamlı ve pozitif yönde ilişkiliydi. Orta ila majör olası ilaç-ilaç etkileşimlerinin varlığı, erkek cinsiyet (p=0,012) ve yetişkin yaş grubu (p=0,019) ile anlamlı ve pozitif olarak ilişkiliydi.
Sonuç: Bu çalışma, COVID-19 tanısı ile hastanede yatan hastalar arasında olası ilaç-ilaç etkileşimleri sıklığının oldukça yüksek olduğunu ortaya koydu. Genel olarak, COVID-19 yatan hasta kliniklerinde olası ilaç-ilaç etkileşimlerinin şiddeti orta düzeyde ve önlenebilir olsa da, kanama riski gibi hayatı tehdit edici sonuçları olabilecek olası ilaç-ilaç etkileşimleri konusunda hekimler özel dikkat göstermelidir.

Anahtar Sözcükler: İlaç Etkileşimleri, Covid-19, Hastaneye Yatış, Favipiravir, Asetilsalisilik asit, Parasetamol

Geliş Tarihi: 03.01.2022 **Kabul Tarihi:** 10.08.2022

ORCID IDs: E.N.Ö.0000-0003-0612-9000,B.S. 0000-0002-6219-9321

Address for Correspondence / Yazışma Adresi: Emine Nur Özdamar, MD Yeditepe University Faculty of Medicine, Department of Medical Pharmacology İnönü Mah. Kayışdağı Cd. 34755 Ataşehir,Istanbul,Türkiye E-mail: nur.ozdamar@yeditepe.edu.tr

doi:http://dx.doi.org/10.12996/gmj.2023.61

INTRODUCTION

Drug-drug interaction (DDI) is defined as the changes in the pharmacological action of a drug in the presence of another drug which is used consecutively or concomitantly (1). DDIs cause a global concern affecting both the healthcare professionals and the society due to increased morbidity and mortality rate of the patients (2, 3). DDIs may be responsible for approximately 1% of hospitalization in the general population, this rate increases up to 2-5% in the elderly (4). DDIs and related adverse drug reactions are generally known to be preventable. However, the fact that a high number of drugs may interact with each other makes it necessary for physicians to have knowledge regarding commonly interacting drugs and improper drug combinations (4,5). Potential DDI (pDDI) term is entitled as the probability that one drug may change another drug's effect in case of using them concurrently (6).

Particularly, polypharmacy is known to be a significant risk factor for pDDIs (7). Although there is no consensus regarding the exact description, five or more drug use (≥5) daily is the most frequent definition. In addition, a drug number of ten or over is named as hyperpolypharmacy which is significantly associated with older age and concomitant co-morbid conditions (8).

COVID-19 is an ongoing pandemic which was firstly identified on January 2020 and caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Old age, high polypharmacy rates and multimorbidities have been found to be significantly associated with COVID-19 infection which may lead to hospitalization, admission to intensive care unit (ICU) or death (9, 10).

In Turkey, according the COVID-19 adult patient treatment guideline published by Ministry of Health, Favipiravir is recommended for COVID-19 cases with hospitalization indication. (https://covid19.saglik.gov.tr/Eklenti/40719/0/covid-rehberierisikinhastayonetimivetedavipdf.pdf)

Particularly, COVID-19 related drugs and concomitantly used drugs of the patients for their co-morbid diseases may enhance the risk for having pDDIs during hospitalization (11). As such, the aim of the present study is to identify the frequency and severity of pDDIs between the COVID-19 treatment options and concomitantly used drugs at COVID-19 inpatient clinics of a public hospital.

METHODS

In the present cross-sectional retrospective study, we analyzed the data of the patients with COVID-19 infection who were hospitalized at inpatient clinics of a public hospital between November 1, 2020 and 15 December 2020. The ethical approval was obtained from the Bakirköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (IRB No: 2021-02-30, January 18, 2021) prior to the study. The files of the patients who met the inclusion criteria of being 18 years and older and being administered drugs at inpatient clinics were included in the present study. The variables such as demographic characteristics (gender, age) and clinical conditions (co-morbidities) of the patients, length of stay in hospital, admission to the intensive care unit (ICU), number of the newly prescribed drugs, number of the drugs that patients concomitantly use for their chronical diseases, total number of drugs, pharmaceutical dosage forms of drugs, number of the pDDIs and risk category and the severity of pDDIs were evaluated.

Analysis of the pDDIs

The frequency, risk category and severity of the pDDIs were assessed according to the Lexi-comp® online drug interaction database which classifies the risk rating levels as A, B, C, D, X category and the severity as minor, intermediate and major (Table 1), (12).

Table 1. Lexi-comp® online interaction risk rating and severity rating categories

Risk Rating	**Description**
A	No evidence of interaction.
B	The two medications may interact with each other, but there is little to no evidence of clinical concern due to their concomitant use.
C	The two medications may interact with each other in a clinically significant manner. The benefits of concomitant use generally outweigh the risks. Monitoring the therapy is recommended.
D	The two medications may interact with each other in a clinically significant manner. Aggressive monitoring and considering therapy modification is recommended.
X	The specified agents may interact with each other in a clinically significant manner. Concomitant use of these agents are contraindicated. Avoiding the combination is recommended.
Severity Rating	**Description**
Minor	The interaction is inappropriate but not medically harmful.
Intermediate	The interaction may worsen the patient's condition. The patient may need additional care.
Major	The interaction may be life-threatening or lead to permanent damage.

Statistical Analysis

The statistical analyses were carried out by using SPSS v25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where appropriate. Categorical data were expressed as percentages. Chi-square ($\chi 2$) test was performed for the comparison of the hyper-polypharmacy (≥ 10 drugs) and moderate-major pDDIs based on the gender, age categories, co-morbidities and ICU admission. A p value less than 0.05 was considered as statistically significant.

RESULTS

Demographic characteristics and co-morbidities of the patients

From November 1 to December 15, 2020, a total of 321 files of the patients with COVID-19 who were hospitalized at inpatient clinics of a public hospital were assessed retrospectively. The mean age of the patients was 57.0 ± 14.4 (range 18-98), with male preponderance (59.5%), (Table 2). Most of the patients were between 45-64 years (45.5%). At least one co-morbid disease was detected in 43.6% of the patient's. The most common co-morbidity was essential hypertension (34%), followed by diabetes mellitus (27.7%) and coronary artery disease (8.7%). The length of stay in hospital varied between 2 to 27 days, with a median of 8 days. More than a half of the patients (59.5%) had a length of stay of 5-9 days. During hospitalization, 35 patients (10.9%) were admitted to the ICU. (Table 2).

Table 2. Demographic characteristics and clinical features of the patients (n=321)

Variables	n (%)
Gender	
Female	130 (40.5)
Male	191 (59.5)
Age categories	
18-44	68 (21.2)
45-64	146 (45.5)
≥65	107 (33.3)
Mean age±SD (years)	57.0 ± 14.4
Number of co-morbidities	
None	181 (56.4)
1	66 (20.6)
2	62 (19.3)
3	12 (3.7)
Co-morbid diseases	
Essential hypertension	109 (34.0)
Diabetes mellitus	89 (27.7)
Coronary artery disease	28 (8.7)
Length of stay in hospital - days	
2-4	26 (8.1)
5-9	191 (59.5)
10-14	73 (22.7)
15-19	23 (7.2)
≥20	8 (2.5)
Admission to the ICU	
Yes	35 (10.9)
None	286 (89.1)
Length of stay in hospital - days [median (min-max)]	8 (2-27)

SD: Standard deviation, ICU: Intensive care unit

Drug utilization characteristics

A total of 2884 drugs which comprise COVID-19 related drugs prescribed at inpatient clinics and concomitantly used drugs of the patients for their co-morbid diseases were administered to patients during the hospital stay.

Average number of drugs per encounter was 9.0±1.9 with a minimum of 2 and a maximum of 17 drugs. Most of the patients used between 5 to 9 drugs (62.9%) totally. According to the dosage forms, tablets were present in all prescriptions (100%), followed by vials (99.7%) and pre-filled syringes (99.4%), (Table 3). Enoxaparin (11.1%) and Paracetamol (11.1%) were the most frequently prescribed drugs, followed by Pantoprazole (11.0%), Favipiravir (10.7%) and N-acetyl cysteine (10.7%). Top 20 drugs used for patients with COVID-19 at inpatient clinics are depicted in Figure 1.

Table 3. Drug utilization characteristics (n=321)

Variables	n (%)
Number of concomitantly used drugs for co-morbid diseases	
None	183 (57.0)
1	42 (13.1)
2-4	86 (26.8)
5-9	10 (3.1)
Number of COVID-19 related drugs	
2-4	2 (0.6)
5-9	276 (86.0)
≥10	43 (13.4)
Total number of drugs	
<5	2 (0.6)
5-9	202 (62.9)
≥10	117 (36.4)
Pharmaceutical dosage forms	
Tablet	321 (100)
Vial	320 (99.7)
Pre-filled syringe	319 (99.4)
Oral drop	177 (55.1)
Ampoule	44 (13.7)
Pre-filled pen	34 (10.6)
Effervescent tablet	4 (1.2)
Capsule	2 (0.6)
Oral suspension	1(0.3)
Sachet	1 (0.3)
Syrup	1 (0.3)
Average number of drugs per encounter (Mean±SD)	9.0±1.9

SD: Standard deviation

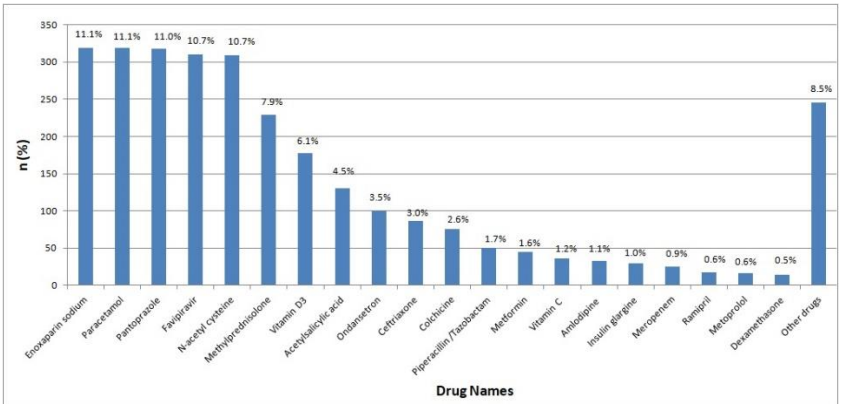

Figure 1. Top 20 drugs used for patients with COVID-19 at inpatient clinics.

Analysis of pDDIs

All of the patients (100%) were prescribed two or more drugs and further analyzed for pDDIs. A vast majority of the patients (99.1%) had at least one pDDI with a maximum of 25 pDDIs. The mean number of pDDIs per patient was 3.9±3.2. One thousand two hundred and seventy one pDDIs were determined of which 45.2% were C category interactions, followed by B category (41.1%) and D category (13.5%), (Table 4). According to the severity, more than a half of the pDDIs (58.7%) were moderate interactions. The most commonly detected pDDIs were between Favipiravir and Paracetamol (B risk category), (24.4%), followed by the pDDIs between Enoxaparin-Acetylsalicylic acid (D risk category), (10.1%) and Methylprednisolone-Acetylsalicylic acid (C risk category), (8.8%) drug pairs. Frequency and the severity of the top 10 pDDIs at the COVID-19 inpatient clinics are depicted at Table 5.

Hyper-polypharmacy (≥10 drugs) was significantly and positively associated with male gender (p=0.023), adult age group (p=0.002) and co-morbid diabetes mellitus (p<0.001) and essential hypertension (p<0.001). The presence of moderate to major pDDIs was significantly and positively associated with male gender (p=0.012), adult age group (p=0.019) (Table 6). Conversely, there was no significant statistical relation of ICU admission with hyper-polypharmacy (p=0.228) and the presence of moderate to major pDDIs (p=0.132), (Table 6).

Table 4. Analysis of pDDIs at COVID-19 inpatient clinics (n=321)

Variables	n (%)
pDDIs	
Yes	318 (99.1)
None	3 (0.9)
Number of pDDIs	
1-4	216 (67.3)
5-9	79 (24.6)
10-19	22 (6.8)
> 20	1 (0.3)
pDDI risk category	
B	522 (41.1)
C	575 (45.2)
D	172 (13.5)
X	2 (0.2)
Severity of pDDIs	
Minor	522 (41.1)
Moderate	747 (58.7)
Major	2 (0.2)
The mean number of pDDIs per patient (Mean±SD)	3.9±3.2.

pDDI: potential drug-drug interaction

Table 5. Frequency and the severity of the most frequent 10 pDDIs at the COVID-19 inpatient clinics (n=1271)

DDIs	Risk category	Estimated clinical outcomes	Severity	Patient management	n (%)
Favipiravir-Paracetamol	B	Favipiravir may increase the serum concentration of paracetamol.	Minor	No action required.	310 (24.4%)
Enoxaparin-Acetylsalicylic acid	D	Agents with antiplatelet properties may increase the anticoagulant effect of Enoxaparin.	Moderate	Cease antiplatelet agents prior to starting enoxaparin. If co-administration is mandatory monitor closely for the risk of bleeding.	128 (10.1%)
Methylprednisolone-Acetylsalicylic acid	C	Salicylates may increase the adverse effect of systemic corticosteroids. (particularly gastrointestinal ulcers and bleeding)	Moderate	Monitor for gastrointestinal ulceration.	112 (8.8%)
Paracetamol-Ondansetron	B	5-HT3 antagonists may decrease the analgesic effect of paracetamol.	Minor	No action required.	100 (7.9%)
Metformin-Pantoprazole	B	Pantoprazole may rise the serum level of Metformin.	Minor	No action required.	46 (3.6%)
Metformin-Methylprednisolone	C	Hyperglisemia associated agents may decrease the therapeutic effect of antidiabetic agents	Moderate	Monitor blood glucose levels more frequently when used concomitantly.	30 (2.4%)
Metformin-Ondansetron	C	Ondansetron may increase the serum level of Metformin	Moderate	Monitor for increased metformin effects when used concomitantly.	21 (1.7%)
İnsulin Glargine-Methylprednisolone	C	Hyperglisemia associated agents may decrease the therapeutic effect of antidiabetic agents	Moderate	Monitor blood glucose levels more frequently when used concomitantly.	21 (1.7%)
Ramipril-Enoxaparin	C	Low molecular weight heparins may increase the hyperkalemic effect of ACE inhibitors.	Moderate	Monitor serum potassium levels closely when used concomitantly.	20 (1.6%)
Vitamin C- Acetylsalicylic acid	B	Acetylsalicylic acid may decrease the serum level of Vitamin C.	Minor	No action required.	18 (1.4%)

5-HT3 antagonists: Serotonin 5-hydroxy tryptamine 3 receptor antagonists, ACE inhibitors: Angiotensin converting enzyme inhibitors.

Table 6. Comparison of the presence of hyper-polypharmacy and moderate-major pDDIs based on patients' demographic characteristics, clinical conditions.

Variables	Hyper-polypharmacy			Moderate to major pDDIs		
	Yes n (%)	None n (%)	p value	Yes n (%)	None n (%)	p value
Gender						
Female	57 (48.7%)	73 (35.8%)		96 (45.5%)	34 (30.9%)	
Male	60 (51.3%)	131 (64.2%)	p=0.023	115 (54.5%)	76 (69.1%)	p=0.012
Age						
18-44	13 (11.1%)	55 (27.0%)		35 (16.6%)	33 (30.0%)	
45-64	55 (47.0%)	91 (44.6%)	p=0.002	100 (47.4%)	46 (41.8%)	p=0.019
≥65	49 (41.9%)	58 (28.4%)		76 (36.0%)	31 (28.2%)	
Co-morbid diseases						
Diabetes mellitus	65 (55.6%)	24 (11.8%)	p<0.001	87 (41.2%)	2 (1.8%)	p<0.001
Essential Hypertension	73 (62.4%)	36 (17.6%)	p<0.001	99 (46.9%)	10 (9.1%)	p<0.001
Coronary artery disease	17 (14.5%)	11 (5.4%)	p=0.005	28 (13.3%)	0 (0%)	p<0.001
Admission to the ICU						
Yes	16 (13.7%)	19 (9.3%)		27 (12.8%)	8 (7.3%)	
None	101(86.3%)	195 (90.7%)	p=0.228	184 (87.2%)	102 (92.7%)	p=0.132

pDDIs: Potential drug-drug interactions, *Chi square test

DISCUSSION

Considering the necessity of multiple drug utilization for the management of COVID-19, it may be an expected outcome to encounter pDDIs in hospitalized patients with COVID-19. Hence, we conducted this cross-sectional retrospective study to reveal the frequency, severity and management of pDDIs in these patients. To the best of our knowledge, the present study is the first to assess the pDDIs in hospitalized COVID-19 cases in Turkey.

In this retrospective analysis of 321 patient data from COVID-19 inpatient clinics, more than a half of the patients were male (59.5%). Similar to our results, several studies from different countries which assessed the pDDIs among hospitalized patients with COVID-19 reported male preponderance over female (11, 13, 14). These finding could be attributed to the evidence suggesting for a protective role of female sex hormones against against SARS-CoV-2 (15). The most frequent age group was between 45-64 years (45.5%). A similar result was also reported by a study from Eastern India, which reported that the hospitalized patients with COVID-19, were mostly middle aged (40.5%), (16). The median length of hospital stay was 8 days in our study. A longer length of hospital stay value (median-11 days) was reported by Cantudo-Cuenca et al., who assessed pDDIs among hospitalized COVID-19 patients in Spain (17).

Average number of drugs per patient in the present study was 9.0±1.9 which is slightly higher than a previous study from Northern Italy assessing the pDDIs among patients with COVID-19 (11). The most commonly used drugs at COVID-19 inpatient clinics were Enoxaparin, Paracetamol and Pantoprazole, with close percentages, respectively. Similar to our result, Manjhi et al., reported Paracetamol and Enoxaparin as amongst the most commonly used agents for hospitalized COVID-19 patients (16). It is known that, there is a trend towards the use of polypharmacy in the management of COVID-19. Particularly, paracetamol, anticoagulants, glucocorticoids, vitamins, antibiotics and N-acetylcysteine, which are among top 20 drugs in our study, is used commonly as adjuvan, supportive and symptomatic therapy strategies for COVID-19 (18-20).

We found a high frequency of the pDDIs (99.1%) among the drugs used for the patients with COVID-19. Several studies from distinct countries reported lower frequency rates of pDDIs (68.0%, 62.5% and 72.9%, respectively) as compared to our study (11, 13, 17). In contrast, a higher prevalence of pDDIs (100%) was reported by Manjhi et al. (16). In terms of severity, moderate interactions were more common (58.7%) in the present study. Our finding was comparable to those reported by Crescioli et al. who found 64.4% moderate pDDIs in hospitalized patients with COVID-19 (21).

The most common pDDI in this study was between favipiravir and paracetamol which has a minor severity. Although, no action is needed for this type of interaction, it would be safer not to exceed the daily dose of paracetamol over 3 g when used concomitantly with favipravir (18).

The second commonly encountered pDDI in our study was between Enoxaparin-Acetylsalicylic acid which combination carries a high risk of bleeding and necessitates intense monitoring. This enhanced risk of bleeding due to coadministration of enoxaparin with acetylsalicylic acid has been also reported by Cattaneo et al., who assessed the pDDIs of patients with COVID-19 at hospital discharge (22). Therefore, if the combination is mandatory, the physician should be very alert regarding the pDDIs and high risk of bleeding.

We found a significant association between the hyper-polypharmacy and male gender, adult age and co-morbid diabetes mellitus and hypertension. In contrast to our results, a study by Sheikh-Taha et al., who evaluated hyper-polypharmacy and pDDIs among older adults, reported significant relationship of hyper-polypharmacy with older ages and co-morbid cardiovascular diseases (8). In addition, there was also a significant association of moderate to major pDDIs with male gender and adult age and no statistical relation with ICU admission. Different from our results, Mahboobipour et al., reported a relationship of moderate-major pDDIs with older age, co-morbid diseases and ICU admission (14).

Since this is a retrospective study, we don't know the outcomes of pDDIs. In addition, our study was carried out with a small number of hospitalized COVID-19 patients in a public hospital for a short period of time. However, we expect that the present study would be guiding for the multi-center studies with larger sample sizes in the future.

In conclusion, the present study revealed that the frequency of pDDIs among hospitalized patients with COVID-19 are quite high. Although the severity of pDDIs at COVID-19 inpatient clinics in general, are moderate and preventable, physicians should pay a particular attention regarding the pDDIs which may have life-threatening consequences such as the risk of bleeding.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. de Oliveira LM, Diel JdAC, Nunes A, dal Pizzol TdS. Prevalence of drug interactions in hospitalised elderly patients: a systematic review. Eur J Hosp Pharm 2021; 28: 4–9.

2. Rosas-Carrasco O, Garcia-Pena C, Sanchez-Garcia P, Varcas-Alarcon, Gutierrez-Robledo LM, Juarez-Cedillo T. The relationship between potential drug-drug interactions and mortality rate of elderly hospitalized patients. Rev Invest Clin 2011; 63 (6): 564-573.

3. Novaes PH, da Cruz DT, Lucchetti ALG, Leite ICG, Lucchetti G. The ''iatrogenic triad'': polypharmacy, drug–drug interactions, and potentially inappropriate medications in older adults. Int J Clin Pharm 2017; 39: 818–825.

4. Letinier L, Cossin S, Mansiaux Y, Amaud M, Salvo F, Bezin J, et al. Risk of drug-drug interactions in out-hospital drug dispensings in France: results from the drug-drug interaction prevalence study. Front Pharmacol 2019; 10: 1-9.
5. Turgeon J, Michaud V. Clinical decision support systems: great promises for better management of patients' drug therapy. Expert Opin Drug Metab Toxicol 2016; 12 (9): 993- 995.
6. Morales-RõÂos O, Jasso-GutieÂrrez L, Reyes-LoÂpez A, Garduño-Espinosa J, Muñoz-HernaÂndez O. Potential drug-drug interactions and their risk factors in pediatric patients admitted to the emergency department of a tertiary care hospital in Mexico. PLoS One 2018; 13(1): e0190882.
7. Weng YA, Deng CY, Pu C. Targeting continuity of care and polypharmacy to reduce drug–drug interaction. Sci Rep 2020; 10: 1–9.
8. Sheikh-Taha M, Asmar M. Polypharmacy and severe potential drug drug interactions among older adults with cardiovascular disease in the United States. BMC Geriatrics 2021; 21: 233.
9. McQueenie R, Foster HME, Jani BD, Katikireddi SV, Sattar N, Pell JP, et al. Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort. PLoS One 2020; 15(8): e0238091.
10. Iloanusi S, Mgbere O, Essien E. Polypharmacy among COVID-19 patients: A systematic review. J Am Pharm Assoc 2021;61: e14-e25.
11. Cattaneo D, Pasina L, Maggioni AP, Giacomelli A, Oreni L, Covizzi A, et al. Drug–drug interactions and prescription appropriateness in patients with COVID-19: a retrospective analysis from a reference hospital in Northern Italy. Drugs Aging 2020; 37: 925–933.
12. UpToDate, Inc. Lexi-Interact Online. https://www.uptodate.com/drug-interactions/#didruglist (Accessed: Nov 2021).
13. Saber-Moghaddam N, Hejazi S, Elyasi S. Potential Drug–Drug Interactions among hospitalized COVID-19 patients admitted to medical wards of a Referral Hospital, North-East of Iran: a cross sectional study. J Pharm Care 2021; 9(2): 88-95.
14. Amir Ali Mahboobipour, Shadi Baniasadi. Clinically important drug–drug interactions in patients admitted to hospital with COVID-19: drug pairs, risk factors, and management. Drug Metabol Pers Ther 2021; 36(1): 9–16.
15. Lipsa A, Prabhu JS. Gender disparity in COVID-19: Role of sex steroid hormones. Asian Pac J Trop Med 2021; 14(1): 5-9.
16. Manjhi PK, Kumar R, Priya A, Rab I. Drug-Drug interactions in patients with COVID-19: A retrospective study at a tertiary care hospital in Eastern India. Maedica 2021; 16(2): 163–169.
17. Cantudo-Cuenca M, Gutiérrez-Pizarraya A, Pinilla-Fernández A, Contreras-Macias E, Fernandez-Fuertes M, Lao Dominguez FA, et al. Drug–drug interactions between treatment specific pharmacotherapy and concomitant medication in patients with COVID-19 in the first wave in Spain. Sci Rep 2021; 11: 12414.
18. Lemaitre F, Solas C, Gregoire M, Lagarce L, Elens L, Polard E, et al. Potential drug-drug interactions associated with drugs currently proposed for COVID-19 treatment in patients receiving other treatments. Fundam Clin Pharmacol 2020; 34: 530-547.
19. De Flora S, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. Faseb J 2020; 34: 13185-13193.
20. Jagiasi B, Nasa P, Chanchalani G, Ahmed A, Kumar AKA, Sodhi K, et al. Variation in therapeutic strategies for the management of severe COVID-19 in India – a nationwide cross-sectional survey. Int J Clin Pract. 2021;75:e14574.
21. Crescioli G, Brilli V, Lanzi C, Burgalassi A, Ieri A, Bonaiuti R, et al. Adverse drug reactions in SARS-CoV-2 hospitalised patients: a case-series with a focus on drug–drug interactions. Intern Emerg Med 2021;16: 697–710.
22. Cattaneo D, Pasina L, Maggioni AP, Oreni L, Conti F, Pezzati L, et al. Drug–drug ınteractions and prescription appropriateness at hospital discharge: experience with COVID-19 Patients. Drugs Aging 2021; 38: 341–346.