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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

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ABSTRACT

Background: Hospitalized corona virus disease 2019 (COVID-19) patients are special population in term of drug-drug interaction (DDI), as they receive various experimental novel medications and also most of them are elderly with various comorbidities and consequently numerous medications. The aim of present study was to assess the prevalence and determinants of potential DDIs in hospitalized COVID-19 patients admitted to the medical ward of a Referral Hospital in North-East of Iran.

Methods: A cross-sectional study was conducted among COVID-19 inpatients between March 2020 and April 2020. Prescribed medication being taken concurrently for at least 24 h were included and checked for DDI using Lexicomp® online drug reference. Data were analyzed using SPSS19.

Results: A total of 88 patients were evaluated. The cardiovascular disease was the most common comorbidity (30.68%). The median number of medications prescribed for each patient was 5. Hydroxychloroquine was the most common prescribed medication for COVID-19 management (92.05%). About two-third (62.5 %) of patients were exposed to at least one potential C (84.09 %) or D (52.27%) DDI and no X DDIs were found. Patients with at least five prescribed medications were at higher risk of having DDI (P = 0.001).

Conclusion: Drug–drug interaction in COVID-19 inpatients was common. Considering these DDIs, clinical pharmacist involvement can be helpful in minimizing the risk of these potentially harmful drug combinations.

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Introduction

Severe acute respiratory syndrome -coronavirus-2 (SARS-CoV-2) is first detected in December 2019 in China, and has been presented as the first pandemic of the century in March 2020 (1). The disease is named as corona virus disease 2019 (COVID-19) and dyspnea, fever, cough, myalgia and other flu-like symptoms are its main presentation (2). Though, it can progress to more severe disease and causes acute respiratory distress syndrome (ARDS), organ failure and death (3). No approved safe and effective treatment have

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been proposed for the management of COVID-19, but there are several therapeutic measures being used off label either based on international or national guidelines or as part of a randomized controlled clinical trial. However, clinicians should be aware of their adverse effects and potential drug interactions with other patients' medications. Serious reactions are associated with these drugs which may overlap with the clinical manifestations of COVID-19. Chloroquine (CLQ)/hydroxychloroquine (HCQ), azithromycin (AZI), and lopinavir/ritonavir (LPV/r) are associated with various adverse effects, including QTc prolongation, torsade de pointes, hepatitis, acute pancreatitis and neutropenia which may be exacerbated in case of drug-drug interactions (4). Drug–drug interactions (DDIs) happens when the effects of one drug is changed by another concomitantly administered drug (5). Based on a systematic review and meta-analysis of observational study, DDI was responsible for the 1.1% hospital admissions and 0.1 % hospital visits (6). It may decline the therapeutic effect of a drug, or increase occurrence of adverse drug reactions (ADRs) and compromised treatment outcomes (7,8). Besides, DDI can increase length of hospital stay and consequently healthcare costs (9,10). Advanced age, polypharmacy and multiple prescribers are the main risk factors for occurrence of potential drug interactions (11). Considering that most patients who have died from COVID-19 were elderly and had underlying health conditions including cardiovascular comorbidities, the risk of drug-drug interaction increases. In this observational cross-sectional study we evaluated the potential drug-drug interactions in hospitalized COVID-19 patients in a teaching hospital, in North-East of Iran.

Methods

This was an observational cross-sectional study, conducted in COVID-19 ward of a teaching hospital between 20 March 2020 and 20 April 2020, were included.

Patients with diagnosis of COVID-19 based on (1) a positive Real-Time Polymerase Chain Reaction (RT-PCR) of the respiratory tract samples, (2) clinical signs/symptoms, (3) imaging findings highly suspicious for COVID-19 (e.g. ground-class pattern in chest X ray) who were admitted to the COVID-19 ward of a teaching hospital were included in this study. Patients discharged before 24 hours were excluded from study.

Patients' charts were reviewed by the clinical pharmacy resident and their demographic and laboratory data including age, sex, COVID-19 RT-PCR of respiratory tract sample, lung CT, and blood or other sample cultures results, and also anti-COVID and other medications were collected in a prepared form.

Prior to the actual data collection, a pretest was done on five patients (not included in this study) to check the practicability of the data collection format and procedures and to assess the performance of data collectors. Then, the drug-drug interactions for each patient were checked based on online Lexicomp® drug interaction checker (12). Patients' medical record was reviewed every 2 days from date of admission to date of discharge to see any added or discontinued treatments. Prescribed drugs being taken concurrently for at least 24 h were included and checked for drug–drug interaction using Lexicomp® drug interaction checker (12). Lexicomp® is medical software which gives evidence-based drug information about DDIs and potential ADRs. It categorizes drug combinations into X (contraindicated), D (Consider therapy modification), C (monitor therapy), and B (No action needed) level of interaction based on the mortality and morbidity probabilities on patients. So, the primary outcome of the study was to determine the number of potential C, D or X DDIs in patient's drug regimen. Determination of associated factors with DDIs could be mentioned as secondary outcome.

The analysis was performed by SPSS software, version 19. Results have been reported as mean± standard deviation or median (range) for normally and non-normally distributed continuous variables, respectively and numbers or percentages for nominal parameters. Fisher's exact test was used to compare proportions between the groups; $p < 0.05$ was considered as significant.

Results

During this one month period, 88 patients in COVID-19 ward were assessed. The mean age of patients was 62.69±18.63 years. Fifty-seven patients were male (64.8%). Lung CT was performed in all patients and it was in consistent with COVID-19 in 85 cases (96.6%). RT-PCR was done in 55 patients which was positive in 55.7% of them (n=49). The mean duration of patients' hospital stay was 8.36±4.39 days. 53.4% of the participants had comorbid conditions. The cardiovascular disease was the most common comorbidity in these patients (n=27, 30.68%), followed by cancer and neurology disorders (n=17, 19.32% for each one) (Table 1).

Table 1. Frequency of concomitant diseases in study population.

Concomitant condition	Number (%)
Cardiovascular	27 (30.68)
Cancer	17 (19.32)
Neurology	17 (19.32)
Diabetes mellitus	12 (13.64)
Renal	12 (13.64)
Pulmonary	9 (10.23)
Gastrointestinal	8 (9.09)
Infections	5 (5.68)
Urology	2 (2.27)
Endocrine	2 (2.27)

Fourteen patients were addicted to inhaled or oral opium (15.91%). The median number of medications prescribed for each patient was 5 (1-10). HCQ was the most common prescribed medication for COVID-19 management (92.05%), followed by AZI (65.91%) and atorvastatin (60.23%). List of medications with potential anti-COVID-19 effect which were used in these patients are summarized in Table 2.

Table 2. Frequency of anti-COVID-19 medication used in study population.

Anti-COVID-19 medication	Number (%)
Hydroxychloroquine	81 (92.05)
Azithromycin	58 (65.91)
Atorvastatin	53(60.23)
Lopinavir/ritonavir	32(36.36)
n-acetylcysteine	36 (40.91)
Colchicine	3 (3.41)
Naproxen	9 (10.23)
Interferon	1 (1.14)

Broad-spectrum antibiotics were used in 58 patients and ceftriaxone and meropenem were the most common used antibiotics (n=32 and 22, respectively) (Table 3). However, just 12 patients had positive bacterial culture.

Table 3. Frequency of broad-spectrum antibiotics used in study population.

Antibiotic	Number (%)
Ceftriaxone	32 (36.36)
Cefepime	9 (10.23)
Ceftizoxime	2 (2.27)
Ceftazidime	1 (1.14)
Cefotaxime	1(1.14)
Meropenem	22(25)
Vancomycin	7 (7.95)
Clindamycin	6 (6.82)
Metronidazole	6 (6.82)
Colistin	1(1.14)
Ciprofloxacin	9 (10.23)
Cotrimoxazole	1(1.14)
Linezolid	1(1.14)
Ampicillin-sulbactam	2(2.27)

Considering the drug-drug interactions in studied population, based on Lexicomp® drug interaction checker (12), 62.5% of patients exposed to at least one potential drug interaction. No X interaction found in these 88 patients. However, 16 D interactions and 19 C interactions were defined. Lopinavir/ritonavir interaction with atorvastatin was the most common D interaction (n=20) and azithromycin with atorvastatin was the most common C interaction (n=40) (Table 4).

Table 4. List of drug-drug interactions in studied population.

Interaction risk rating	Medications	Number (%)	Reliability Rating	
D	**Atorvastatin/Kaletra®**	20(22.73)	Fair	Increased risk of myopathy or rhabdomyolysis
	Methadone/ Kaletra®	4(4.55)	Fair	Increased methadone exposure
	Methadone/valproate	2(2.27)	Fair	enhanced the CNS depressant effect
	Methadone/azithromycin	5(5.68)	Fair	Increased risk of QT-interval prolongation
	Atorvastatin/carbamazepine	1(1.14)	Fair	Increased risk of myopathy or rhabdomyolysis
	Atorvastatin/phenytoin	1(1.14)	Fair	Decreased atorvastatin exposure
	Kaletra®/carbamazepine	2(2.27)	Fair	Decreased lopinavir exposure/increased carbamazepine exposure
	phenytoin/Kaletra®	2(2.27)	Fair	Decreased lopinavir & phenytoin exposure
	Risperidone/carbamazepine	1(1.14)	Good	Decreased risperidone exposure
	Risperidone/phenytoin	1(1.14)	Good	Decreased risperidone exposure
	Chlordiazepoxide/ Kaletra®	1(1.14)	Fair	Increased chlordiazepoxide exposure
	Methadone/levetiracetam	1(1.14)	Fair	enhance the CNS depressant effect
	Atorvastatin/rifampin	1(1.14)	Good	Increased/decreased atorvastatin exposure
	Methadone/rifampin	1(1.14)	Good	decrease the serum concentration of Methadone
	Colchicine/azithromycin	2(2.27)	good	Increased colchicine exposure
	Colchicine/ Kaletra®	1(1.14)	good	Increased colchicine exposure
C	**Atorvastatin/azithromycin**	40(45.45)	Fair	Increased risk of myopathy or rhabdomyolysis
	Methadone/hydroxychloroquine	10(11.36)	Fair	Increased risk of QT-interval prolongation
	Metoprolol//hydroxychloroquine	1(1.14)	good	Increased metoprolol exposure
	Risperidone/ Kaletra®	1(1.14)	Good	Increased risperidone exposure
	Hydroxychloroquine/ciprofloxacin	3 (3.41)	Fair	May enhance the hyperglycemic effect
	Hydroxychloroquine/haloperidol	3(3.41)	Fair	Increased risk of QT-interval prolongation
	Colchicine/digoxin	1(1.14)	Fair	Increased risk of myopathy or rhabdomyolysis
	Hydroxychloroquine/digoxin	2(2.27)	Fair	Increased digoxin exposure
	Ceftriaxone/warfarin	1(1.14)	Fair	Increased risk of bleeding
	Atorvastatin/spironolactone	1(1.14)	Fair	enhanced the adverse/toxic effect of Spironolactone
	Hydroxychloroquine/cyclosporine	1(1.14)	Fair	Increased cyclosporine exposure
	Hydroxychloroquine/octerotide	1(1.14)	Fair	May enhance the hyperglycemic effect
	Atorvastatin/digoxin	1(1.14)	Fair	Increased digoxin exposure
	Azithromycin/digoxin	1(1.14)	Excellent	Increased digoxin exposure
	Methadone/ciprofloxacin	1(1.14)	Fair	Increased risk of QT-interval prolongation
	Vancomycin/naproxen	1(1.14)	Good	Increased vancomycin exposure/nephrotoxicity
	Amlodipine/calcium carbonate	1(1.14)	Excellent	Diminished the therapeutic effect of amlodipine
	Azithromycin/ondansetrone	2(2.27)	Fair	Increased risk of QT-interval prolongation
	Atorvastatin/colchicine	2(2.27)	Fair	Increased risk of myopathy or rhabdomyolysis

There was no significant difference in the DDI rate regarding to age, sex, presence of co-morbidities and length of hospital stay. However, DDI occurrence was significantly related to increase in number of drugs (polypharmacy) (P = 0.001) (Table 5). Five patients died during hospital admission, no potential DDIs were found in two patients, one C DDI in two patients and one C and one D DDI in the last one. All of them died because of exacerbation of their COVID-19 infection course and not related to drug adverse reaction or interaction.

Table 5. Statistical association of variables with drug–drug interaction.

Variable	Category	DDI		P value[1]
		yes	No	
Sex	**Male**	36	21	1
	Female	19	12	
Age (y)	**<60**	14	15	0.061
	60-74	19	12	
	≥75	22	6	
Comorbidities	**No**	23	18	0.276
	Yes	32	15	
Hospital stay (days)	**<10**	36	25	0.349
	≥10	19	8	
Number of medications	**<5**	9	17	0.001*
	≥5	46	16	

Discussion

The main purpose of this study was assessing potential drug-drug interactions in COVID-19 patients during one month period. In this study, 62.5 % of the patients were exposed to at least one potential DDI (C or D). In this study polypharmacy (taking five drugs or more) was recognized as predictor for the occurrence of DDI (P = 0.001). The risk for developing drug interactions should not essentially prevent use of experimental treatment for COVID-19, as they are frequently manageable and are not always problematic. Balancing the risk of 'theoretical' drug interactions against the benefit of new therapies is the important point. Actually, all unnecessary medication should be stopped to minimize the risk of interactions. This is possible when prescribers are aware of the presence of these potential drug-drug interactions, and the importance of a full drug history review even for ill patients who are unable to give a detailed history. In this study, we tried to represent the potential drug-drug interactions the COVID-19 patients' population to emphasize the importance of getting a precise drug history from patients or their accompanying person. The mean (±SD) number of drugs prescribed per patient in this study was 5.34 (±1.79) which is modestly lower than previous studies on drug-drug interactions (13-16). However, most of that studies were belonged to the elderly population, and when we just considered patients aged higher than 60y (59 patients), the mean number of prescribed medications per patient increased to 7.1±2.4 in our study as well. In this study cardiovascular disease was the most common comorbidity, followed by cancer and neurologic disorders. A meta-analysis by Yang et al. on prevalence of comorbidities in COVID-19 patients also reported hypertension as most common concomitant disease, however followed by diabetes and respiratory disorders (17). This may be due to differences in the study population. Most of included studies to this meta-analysis belonged to China and the prevalence of hypertension and diabetes in their general population is also consistent with COVID-19 population (18,19). In this study, 62.5 % of the patients were exposed to at least one potential DDI (C or D). As to the best of our knowledge no study defined the DDI prevalence in COVID-19 population, we just compared our findings with other studies on DDI in other populations which our results were in line with the findings by Teka et al., (12), Pasina et al., (20) and Lea et al., (21), which reported a prevalence of 62.2%, 63.5, 60.5 % potential DDIs respectively in elderly population. In contrast, lower prevalence of DDIs was reported from other studies focusing on elderly outpatients (22-24). This shows that drug interactions are more common in inpatients setting perhaps due to the difference in number of drugs prescribed per patient.

As Kumar et al., mentioned in their study, remdesivir is metabolized by CYP 2C8, 3A4 and 2D6 and their inhibitors and inducers can affect its serum concentration and efficacy (25). However, it worth mentioning that remdesivir was not confirmed for the treatment of COVID 19 at the time of our study and was not available in Iran. Thus we didn't mention the potential DDIs between remdesivir and other drugs in this study. The interaction between azithromycin and atorvastatin was the most common reported DDI. Use of azithromycin together with atorvastatin should be

considered with extra caution. Although this combination is usually considered of lower risk than combinations including clarithromycin, or erythromycin, interactions with azithromycin have been also reported and patients should be monitored more closely for evidence of atorvastatin toxicity (e.g., muscle aches or pains, renal dysfunction, etc.) (12). Some case reports have described patients with rhabdomyolysis attributed to an interaction between azithromycin and simvastatin or lovastatin (26, 27). Additionally, an analysis of the WHO Collaborative Centre for International Drug Monitoring database (VigiBase) noted 58 reported cases of azithromycin-statin interactions (versus 118 for clarithromycin-statins, and 36 for erythromycin-statins), in which atorvastatin (24 cases) were the most commonly involved statins (28). The mechanism of this interact with a statin is unclear, as azithromycin is generally considered not to be a significant inhibitor of CYP3A4-mediated metabolism or of SLCO1B1 (OATP1B1)-mediated statin uptake (29-31).

The interaction between Kaletra® and atorvastatin was the most common D level interaction, occurred during this one month period. Based on Lexicomp® atorvastatin should be start with the lowest possible dose and patient should be monitor for signs and symptoms of toxicity (e.g., myalgia, rhabdomyolysis, liver function test abnormalities, etc.) (12). Moreover, one published case report describes development of rhabdomyolysis in a patient treated with atorvastatin and lopinavir/ritonavir, although clarithromycin was also used and may have contributed to suspected increases in atorvastatin concentrations (32). The mechanism of this interaction is the inhibition of atorvastatin metabolism/elimination by the protease inhibitor (likely via CYP3A4 inhibition, although transporter-related or other mechanisms may also be involved), leading to increased atorvastatin concentrations (12). Kumar et al also mentioned that LPV/RPV is a CYP 3A4 substrate and inhibitor, so it can result in serious DDI with drugs such as atorvastatin, dexamethasone and hydroxychloroquine (HCQ) (25).

QT interval prolongation is a major concern in COVID-19 patients treating with various medications. Concomitant use of medications that prolong the QTc interval may further increase the risk for severe toxicities, but evidence about the risks with such combinations is limited. Azithromycin is considered to have a moderate risk of significant QT prolongation or TdP (33-36). The same risk is reported by other highly used medication in COVID-19 patients like methadone. So, if combined use of them is necessary, QTc interval prolongation and arrhythmias (including torsade's de pointes) should be monitored. HCQ also potentially can induce this ADR. Its use in patients with concomitant cardiovascular diseases should be considered carefully not only as a possible direct myocardial toxicity but also as a drug interaction that can enhance the side effects on the cardiac conduction system and therefore on the cardiac rhythm (37). Patients with other risk factors (e.g., older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these potentially life-threatening toxicities (12).

Kaletra is a strong CYP3A4 inhibitor which could meaningfully increase the serum concentration of CYP3A4 substrates like methadone and consequently put the patient at higher risk of its adverse reaction (12). This potential interaction occurred in 4 cases out of 88 evaluated patients. Brandariz-Nunez et al., mentioned that there are some risk factors that increase the risk of potential DDIs including older age, ICU admission, previous illnesses and dyslipidemia (38).

Another interesting interaction which just happened in one patient on anti-TB regimen, was between rifampin and atorvastatin. Rifampin inhibition of organic anion-transporter polypeptide 1B1 (OATP1B1)-mediated uptake of atorvastatin by hepatocytes can result in increased atorvastatin (and active metabolite) exposure. On the other hand, decrease in atorvastatin (and active metabolite) concentrations could happen by likely induction of CYP3A4 and p-glycoprotein by rifampin leading to increased atorvastatin metabolism and excretion. Simultaneous co-administration of atorvastatin with rifampin is recommended when concurrent therapy is required. Delayed administration of atorvastatin following administration of rifampin has been associated with significant reduction in atorvastatin plasma concentrations (12,39).

Two reported case are also available regarding the use of HCQ with rifampicin. It increased HCQ clearance and the severity of lupus in these patients. However, this interaction did not occur in our study population (40). Most of beta-blockers like metoprolol had moderate interaction with HCQ, so it is necessary to monitor blood pressure closely during therapy (40). This interaction occurred in 3 patients during study. Interaction with digoxin necessitates consideration as it can increase digoxin levels and consequently increasing the risk of digoxin toxicity, which happened in two patients in this study period.

The COVID-19 treatments with the most risk for coadministration with antipsychotics are chloroquine, hydroxychloroquine, azithromycin, and lopinavir/ritonavir. This kind of interactions are reported in 4 patients (41). Management of some potential interactions, like colchicine with azithromycin or Kaletra®, which found in some of the cases, depends on drug brand, indication, and hepatic and renal function status. Azithromycin as a P-glycoprotein/ABCB1 Inhibitor and Kaletra® as a strong CYP3A4 Inhibitor may increase the serum concentration of colchicine and based on abovementioned factors the dose of colchicine should be adjusted (12). In this study polypharmacy (taking

five drugs or more) was recognized as predictor for the occurrence of DDI (P = 0.001). Some other studies have also proposed the same idea (5,13,16, 23, 42-49). For example, Mendes-nett et al., reported that the potential drug interaction risk in patients who are taking 2–3, 4–5 and 6–7 medications was 39, 88.8 and 100 %, respectively (44). Moreover, we found a near significant difference between numbers of potential DDIs in various age groups. This is as expected; as the use of many medications in the elderly is unavoidable due to the comorbidities they have which increases the risk of DDI occurrence.

Many of the potential DDI in COVID-19 patients can be avoided with close patient monitoring or the use of alternative therapeutic agents and omission of unnecessary medications. However, it may be difficult for clinicians to remember the multiple DDIs and their clinical significance. Clinical pharmacist can play a role in identification and monitoring of potential DDIs. The present study provides a preliminary insight into the prevalence of potential DDIs in COVID-19 inpatients. In addition, polypharmacy was proposed as a risk factor for the occurrence of DDI which have been observed in other studies. However, the study has some limitations. The study was performed on small number of hospitalized COVID-19 patients for a short period of time. Second, being a cross sectional study which was carried out at one-time point, it was not possible to see the outcome of the potential DDI or the actual occurrence of the interactions from a clinical viewpoint. Further longitudinal studies with larger sample size are necessary for better judgment.

Based on this study, about two third of COVID-19 patients are exposed to at least one potential DDIs. Moreover, patients on five or more medications needs close monitoring as they are at higher risk of having DDIs. Identification and prevention of potentially dangerous DDIs is crucial in this group of patients and clinical pharmacists' intervention can help the clinicians in this context.

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