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Clinically important drug–drug interactions in patients admitted to hospital with COVID-19: drug pairs, risk factors, and management

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19) is an emerging viral infection without any approved treatment. Investigational therapies for COVID-19 may cause clinically important drug–drug interactions (DDIs). We aimed to study potential DDIs (pDDIs) and their risk factors in COVID-19 patients admitted to the hospital.

Methods: We conducted a cross-sectional study in a tertiary respiratory hospital dedicated to COVID-19 patients. The Lexi-Interact database was used to investigate clinically important pDDIs. The database output including interacting drug pairs, risk rating, reliability rating, mechanism, and management was evaluated. Associations between the occurrence of pDDIs and probable risk factors were assessed by logistic regression analysis.

Results: Medical charts of 227 patients were reviewed. About 38% of the patients had at least one clinically important pDDI. More than half of the interactions were between protease inhibitors (lopinavir/ritonavir) and regularly prescribed medications for the management of comorbidities or COVID-19 symptoms (e.g., atorvastatin, alprazolam, salmeterol, and tamsulosin). Ischemic heart disease, chronic respiratory diseases, and ICU admission were significantly associated with the occurrence of pDDIs.

Conclusions: We recommend considering the risk factors for the emergence of clinically important DDIs in the pharmacotherapy of COVID-19 patients. Using an alternative medication or dose adjustments may be required in high-risk patients.

Keywords: COVID-19; drug–drug interaction; risk factor.

Introduction

The Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) characterized it as a pandemic on 11 March 2020 [1]. Although the disease is not severe in most patients [2], it may progress to serious illness and hospitalization particularly in the elderly and those with underlying diseases [3].

There is not yet any approved drug or vaccine to treat COVID-19 and treatment is principally supportive [4]. However, medications approved for other viral diseases such as Ebola, HIV, and influenza are being experimentally applied against COVID-19 [5, 6]. American Society of Health-System Pharmacists (ASHP) has provided a list of COVID-19-related treatments (including antiviral agents, supportive agents, and other medications) and the evidence for them [7]. It is estimated that as many as 800 clinical trials are being planned or performed worldwide to investigate these treatments [5].

Meanwhile, the scientists and clinicians are evaluating different therapies to discover the most effective treatments for COVID-19, they should also consider developing data on adverse effects and potential drug–drug interactions (pDDIs) [8]. The pDDIs may occur between the main treatments and the medications for the management of the wide spectrum of clinical symptoms of COVID-19 and/or underlying medical comorbidities [9]. Recently, Lemaitre et al. described pDDIs between experimental COVID-19 therapies and other medications [10]. However, data on pDDIs in COVID-19 patients in real practice are not available. We designed the current study to investigate pDDIs and their risk factors in COVID-19 patients admitted to the hospital.

Materials and Methods

Study design, setting, and participants

This retrospective cross-sectional study was carried out in Masih Daneshvari hospital, a respiratory center dedicated to COVID-19 patients in Tehran, Iran. COVID-19 patients admitted to the hospital from

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12–26 March 2020 were included in the study. COVID-19 cases were confirmed by polymerase chain reaction (PCR) test according to the WHO case definition [1]. The Ethical Review Board of the National Research Institute of Tuberculosis and Lung Diseases approved the study protocol.

Data collection

The data were collected from the medical records of the patients under the supervision of a clinical pharmacologist. Age, sex, body mass index (BMI), past medical history, length of hospital stay, intensive care unit (ICU) admission (directly or after admission to the ward), patients' outcome (discharge or death), and the medications prescribed 24 h after admission (within 24 h of admission, the prescriptions are usually subject to modification) were gathered. The medications prescribed before admission were included if they were continued 24 h after admission. Patients who stayed in the hospital for less than 24 h were excluded.

The Lexi-Interact database (Lexicomp®, Wolters Kluwer, Hudson, OH, USA, available on UpToDate, 2020) was applied to assess pDDIs. The Lexi-Interact database is an interaction analysis tool, which can identify possible interactions between drug pairs in a patient. The result of the analysis includes risk and reliability ratings scales. The output of the database also recommends patient management and discusses the probable mechanism of the interaction [11, 12].

Risk rating reflects both the level of urgency and the nature of actions necessary to respond to an interaction [12]. Based on the risk rating, the interactions are categorized into five categories including A (no known interaction), B (no action needed), C (monitor therapy), D (modify regimen), and X (avoid combination) [11]. Reliability rating indicates the quantity and nature of documentation for an interaction and is scaled as excellent (E), good (G), or fair (F) [12].

Data analysis

Data were entered into Statistical Package for Social Science version 22.0 (SPSS 22.0) for Windows (SPSS, Chicago, IL, USA). Both descriptive and analytical analyses were performed on the data. Due to the low clinical importance of interactions with a risk rating of A, B, and C, only interactions with D and X scales were considered for further analysis. The interactions with excellent, good, and fair levels of evidence were included. Although available evidence for fair interactions is poor, they should be suspected because of pharmacologic considerations or good evidence for an interaction of pharmacologically similar drug [13].

Descriptive analyses of the variables were expressed as mean, standard deviation [SD], median, interquartile range [IQR], and percentage as appropriate. The association between the occurrence of pDDIs and probable risk factors was assessed using logistic regression analysis. The dependent variable was defined as exposure to at least one D or X interaction. Patient's sex, age, common comorbidities (hypertension, obesity, diabetes, ischemic heart disease [IHD], chronic respiratory diseases [CRDs], neoplasms), and ICU admission were taken as the covariates. At first, univariate logistic regression analysis was carried out. Variables with a significant univariate p-value (<0.05) were further assessed by multivariate analysis.

Results

Demographics and clinical presentation

Two hundred and sixty-two medical charts of patients with confirmed COVID-19 were evaluated. Thirty-five patients were excluded due to the length of hospital stay (less than 24 h). Table 1 shows the demographic and clinical characteristics of the patients. Of the total study population, 60.8% were male. A median number of eight medications (IQR, 6–9) were administered for the patients. At least one comorbidity was detected in 67.8% of

Table 1: Demographic and clinical characteristics of the patients.

Study population	n (%)
Number of patients	227
Age, mean (SD), years	57.7 (± 15.0)
Hospital stay, median (IQR), days	5 (4–8)
Number of drugs, median (IQR)	8 (6–9)
Sex	
Male	138 (60.8%)
Female	89 (39.2%)
ICU admission (directly or after admission to the ward)	40 (17.6%)
Death	21 (9.3%)
Chief complaint	
Fever	35 (15.4%)
Cough	45 (19.8%)
Dyspnea	128 (56.4%)
Fatigue or myalgia	19 (8.4%)
Any comorbidity ^a	154 (67.8%)
Hypertension	69 (30.4%)
Obesity (BMI ≥ 30)	63 (27.8%)
Diabetes	54 (23.8%)
Ischemic heart disease	31 (13.7%)
Chronic respiratory diseases (Asthma/COPD)	15 (6.6%)
Neoplasms	10 (4.4%)
Diseases of the genitourinary system	9 (4.0%)
Nervous system disease	8 (3.5%)
Other endocrine, nutritional and metabolic diseases ^b	7 (3.1%)
Other diseases of the circulatory system ^c	7 (3.1%)
Diseases of the musculoskeletal system and connective tissue	5 (2.2%)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	4 (1.8%)
Mental and behavioral disorders	3 (1.3%)
Diseases of the digestive system	2 (0.9%)
Certain infectious and parasitic diseases	1 (0.4%)

^aUncommon comorbidities were classified according to the International Classification of Diseases by WHO (ICD-10). ^bNot including diabetes and obesity. ^cNot including hypertension and ischemic heart disease.

Figure 1: Number of potential drug-drug interactions (pDDIs) in different risk rating categories (A, B, C, D, X) and the number of patients exposed to each category.

the patients. Hypertension (30.4%) was the most common comorbidity followed by obesity (27.8%) and diabetes (23.8%).

Drug–drug interactions

Figure 1 shows the number of pDDIs in each category and exposed patients. Interactions with the risk rating of D and X were 17.8% of total pDDIs (161 of 904). About 38% of the patients (86 of 227) were exposed to at least one D or X interaction.

Drug combinations, frequency, reliability rating, mechanism, and applicable recommendations for D and X interactions are shown in Tables 2 and 3, respectively. Of the total pDDIs with the risk rating of D and X, 23.6% were unique drug pairs (the interaction occurred one time) (Supplementary Material, Appendix 1). The most frequent interactions were between lopinavir/ritonavir and commonly used medications metabolized by cytochrome P450 3A4 (CYP3A4) such as atorvastatin and alprazolam in the D category and salmeterol/fluticasone and tamsulosin in the X category. The reliability rating of 18% of D and X interactions was good and excellent.

Risk factors

In univariate logistic regression analysis, the occurrence of D and X pDDIs was significantly associated with age, four comorbidities (hypertension, diabetes, IHD, CRDs), and ICU admission as an indicator of COVID-19 severity. Multivariate analysis showed the independent predictors of occurrence of pDDIs are IHD (OR: 4.6, [95% CI: 1.7–12.7],

$p=0.003$), CRDs (OR: 3.5, [95% CI: 1.0–12.2], $p=0.045$), and ICU admission (OR: 3.3, [95% CI: 1.4–6.7], $p=0.004$) (table 4).

Discussion

Infection control measures and supportive cares are currently the main clinical management for COVID-19. However, some medications are being used based on the results of laboratory, animal, and clinical studies [7]. The current study is the first to retrospectively identify risk rating, frequency, reliability rating, mechanism, and clinical management of pDDIs in hospitalized patients with COVID-19. We found that 37.9% of COVID-19 patients were exposed to at least one D or X pDDI during the hospital stay. More than half of pDDIs occurred between lopinavir/ritonavir (branded as Kaletra) and a medication metabolized by CYP3A4 (such as atorvastatin, alprazolam, salmeterol, and tamsulosin). Additive interactions between antiplatelets/nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulants were the second common pDDI in COVID-19 patients.

Lopinavir, a protease inhibitor, is widely used for the treatment of HIV. It is combined with ritonavir, another protease inhibitor, which inhibits the CYP3A4 enzyme and increases the half-life of lopinavir [14]. Lopinavir/ritonavir has activity against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) both *in vitro* and in animal models [15, 16]. An open-label, randomized, phase 2 trial revealed the efficacy and safety of lopinavir/ritonavir combined with interferon beta-1b and ribavirin in the treatment of hospitalized patients with COVID-19 [17]. However, according to ASHP evidence assessment, lopinavir/ritonavir efficacy for the treatment of COVID-19 has not been established [7]. Despite low evidence of efficacy, it is prescribed in certain low- and middle-income countries due to its cost and accessibility. Both lopinavir and ritonavir have important DDIs due to inhibition of CYP3A4 [18].

Our results show that HMG-CoA reductase inhibitors (atorvastatin, rosuvastatin) are the most frequent interacting medications with lopinavir/ritonavir in our patients. Some studies revealed coadministration of different protease inhibitors with atorvastatin increased the area under the concentration–time curve (AUC) of atorvastatin from 1.7- to 9.4-folds (depending on the type of protease inhibitor) [19, 20]. Reducing atorvastatin dose to 20 mg/day and monitoring for signs and symptoms of its toxicity [myalgia, rhabdomyolysis, and liver function test (LFT) abnormalities] should be taken into account when a protease

Table 2: Drug combinations, frequency, reliability rating, mechanism, and recommendations for D interactions (modify regimen) based on Lexi-Interact database [11, 12].

Drug combination	n	Re ^a	Mechanism/effect	Recommendations
Lopinavir/ Ritonavir + Atorvastatin	32	F	CYP3A4 inhibitors ^b may increase the serum concentration of atorvastatin	Start with the lowest possible atorvastatin dose, monitor for signs and symptoms of toxicity
Aspirin + Enoxaparin	13	F	Antiplatelet agents may enhance the anticoagulant effect of Enoxaparin	Monitor closely for signs and symptoms of bleeding
Lopinavir/Ritonavir + Alprazolam	10	G	CYP3A4 inhibitors may increase the serum concentration of alprazolam	Consider using an alternative
Clopidogrel + Enoxaparin	5	F	Antiplatelet agents may enhance the anticoagulant effect of enoxaparin	Monitor closely for signs and symptoms of bleeding
Lopinavir/ Ritonavir + Dexamethasone	5	F	CYP3A4 inhibitors may increase the serum concentration of dexamethasone	Monitor for increased adverse effects of dexamethasone, consider dose reduction
Lopinavir/ Ritonavir + Prednisolone	5	F	CYP3A4 Inhibitors may increase the serum concentration of prednisolone	Monitor for increased adverse effects of prednisolone, consider dose reduction
Lopinavir/ Ritonavir + Rosuvastatin	5	F	CYP3A4 Inhibitors may increase the serum concentration of rosuvastatin	Start with the lowest possible rosuvastatin dose, monitor for signs and symptoms of toxicity
Naproxen + Enoxaparin	4	F	NSAIDs ^c may enhance the anticoagulant effect of enoxaparin	Monitor closely for signs and symptoms of bleeding
Naproxen + Heparin	4	F	NSAIDs may enhance the anticoagulant effect of heparin	Decrease the dose of heparin or NSAIDs
Ibuprofen + Enoxaparin	3	F	NSAIDs may enhance the anticoagulant effect of enoxaparin	Monitor closely for signs and symptoms of bleeding
Indomethacin + Heparin	3	F	NSAIDs may enhance the anticoagulant effect of heparin	Decrease the dose of heparin or NSAIDs
Lopinavir/Ritonavir + Fentanyl	3	F	CYP3A4 inhibitors may increase the serum concentration of fentanyl	Monitor for increased adverse effects of fentanyl, consider dose reduction
Lopinavir/Ritonavir + Quetiapine	3	F	CYP3A4 inhibitors may increase the serum concentration of quetiapine	Consider using an alternative or reduce the quetiapine dose to one-sixth of the original dose
Carbamazepine + Lopinavir/ Ritonavir	2	F	Carbamazepine may decrease the serum concentration of lopinavir	Use a twice-daily lopinavir/ritonavir regimen, monitor for the reduced effect of lopinavir/ritonavir
Clopidogrel + Heparin	2	F	Antiplatelet agents may enhance the anticoagulant effect of heparin	Decrease the dose of heparin or clopidogrel
Indomethacin + Enoxaparin	2	F	NSAIDs may enhance the anticoagulant effect of enoxaparin	Monitor closely for signs and symptoms of bleeding
Midazolam + Fentanyl	2	F	Increased CNS depressant effects	Close monitoring for adverse effects
Propofol + Fentanyl	2	F	Increase CNS depressant effects	Close monitoring for adverse effects
Lopinavir/ Ritonavir + Chlordiazepoxide	2	F	CYP3A4 inhibitors may increase the serum concentration of chlordiazepoxide	Monitor for increased adverse effects of chlordiazepoxide
Lopinavir/Ritonavir + Digoxin	2	G	Ritonavir may increase the serum concentration of digoxin	Reduce the digoxin dose (30–50%) or the dosing frequency, monitor digoxin levels
Lopinavir/Ritonavir + Oxycodone	2	F	CYP3A4 inhibitors may increase the serum concentration of oxycodone	Monitor for increased adverse effects of oxycodone

^aReliability (Re) was scaled as excellent (E), good (G), and fair (F). ^bLopinavir/ritonavir is a strong inhibitor of CYP3A4. ^cNonsteroidal anti-inflammatory drugs. Unique drug pairs are shown in the Supplementary Material, Appendix 1.

inhibitor is used concomitantly [21]. However, differentiation between signs and symptoms of HMG-CoA reductase inhibitors toxicity and COVID-19 is challenging because myalgia and abnormal LFT can also be seen in patients with COVID-19 [9, 22]. Rosuvastatin also has the same interaction with protease inhibitors and its dose should not be exceeded than 10 mg/day when coadministered with lopinavir/ritonavir [23]. Rhabdomyolysis is a serious consequence of this interaction, which was reported in

patients who received lopinavir/ritonavir with atorvastatin or rosuvastatin [24, 25].

Anxiolytic/hypnotic/sedative agents such as alprazolam, chlordiazepoxide, and midazolam were administered in our patients. According to the Lexi-Interact database, evidence for the interaction of alprazolam or midazolam with lopinavir/ritonavir is rated as good and excellent; respectively, in terms of reliability. Other benzodiazepine agents that are less expected to interact with protease

Table 3: Drug combinations, frequency, reliability rating, mechanism, and recommendations for X interactions (avoid combination) based on Lexi-Interact database [11, 12].

Drug combination	n	Re ^a	Mechanism/effect	Recommendations
Lopinavir/Ritonavir + Fluticasone/ Salmeterol	7	F	CYP3A4 inhibitors ^b may increase the serum concentration of salmeterol	Avoid concomitant use or monitor for adverse effects of salmeterol
Lopinavir/Ritonavir + Tamsulosin	4	G	CYP3A4 Inhibitors may increase the serum concentration of tamsulosin	Avoid concomitant use
Ipratropium Bromide/ Salbutamol + Promethazine	2	F	Increase the anticholinergic effects	Avoid concomitant use or monitor for anticholinergic related toxicity
Lopinavir/Ritonavir + Midazolam	2	E	Protease Inhibitors may increase the serum concentration of midazolam	Avoid concomitant use or reduce doses of intravenous midazolam particularly if multiple doses are used

^aReliability (Re) was scaled as excellent (E), good (G), and fair (F). ^bLopinavir/ritonavir is a strong inhibitor of CYP3A4. Unique drug pairs are shown in the Supplementary Material, Appendix 1.

Table 4: Logistic regression analysis for the risk factors of D and X interactions.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age, years				
≥ 60	3.2 (1.8–5.6)	<0.01	1.8 (1.0–3.4)	0.07
< 60				
Sex				
Male	0.9 (0.5–1.6)	0.72	–	–
Female				
Comorbidity				
Hypertension	3.7 (2.0–6.6)	<0.01	1.6 (0.8–3.4)	0.18
Obesity	1.4 (0.7–2.6)	0.31	–	–
Diabetes	2.6 (1.4–4.9)	<0.01	1.5 (0.7–3.2)	0.26
IHD ^a	7.4 (3.0–18.1)	<0.01	4.6 (1.7–12.7)	<0.01
CRDs ^b	3.6 (1.2–10.9)	0.02	3.5 (1.0–12.2)	0.04
Neoplasms	2.6 (0.7–9.4)	0.15	–	–
ICU admission				
Yes	3.0 (1.5–6.1)	<0.01	3.3 (1.4–6.7)	<0.01
No				

Variables with univariate p-values of less than 0.05 were included in multivariate analysis. ^aIschemic heart disease. ^bChronic respiratory diseases.

inhibitors (e.g. lorazepam, oxazepam, temazepam) can be administered instead of alprazolam [26]. Inhibition of CYP3A4, which is responsible for midazolam metabolism in the liver and intestines, elevates the serum concentration of midazolam. Severe prolonged sedation and increased length of hospital stay were reported among patients receiving a combination of a protease inhibitor and intravenous midazolam [27]. However, another study showed that clinical outcomes of HIV patients (on protease inhibitors regimen) who received intravenous midazolam for procedural sedation and those who received diazepam (that is less likely to interact with protease inhibitors) were similar [28]. Considering all the reports, this interaction is

categorized as X in terms of risk rating and the combination should be administered with caution. A dose reduction of intravenous midazolam may be required [29].

SARS-CoV-2 may affect the cardiovascular system and lead to myocardial injury, acute heart failure, or worsening preexisting cardiovascular disease [30]. Therefore, the interaction of cardiovascular agents with investigational medications for COVID-19 should be mentioned. In the current study, nondihydropyridine calcium channel blockers (diltiazem), cardiac glycosides (digoxin), antiarrhythmic agents (amiodarone, lidocaine), and isosorbide dinitrate had D or X interactions with lopinavir/ritonavir. Metabolism inhibition of nondihydropyridine calcium channel blockers may elevate their serum concentration and the risk of AV nodal blockade. Monitoring the toxicity of calcium channel blockers and a 50% dose reduction of diltiazem may be required [31]. The mechanism of D interaction between lopinavir/ritonavir and digoxin is probably due to inhibition of P-glycoprotein transporter and reduction of digoxin renal clearance by ritonavir [32]. Reducing digoxin dose (30–50%) or dosing frequency as well as monitoring digoxin levels is recommended [33]. Lopinavir/ritonavir may enhance the serum concentration of amiodarone and subsequently its QTc-prolonging effect. This combination should be avoided when possible, if not, a dose reduction and serial ECG monitoring is recommended [34]. A combination of amiodarone and azithromycin should also be cautioned in COVID-19 patients due to the QTc prolongation synergism effect. Our previous study showed that DDIs are a risk factor for prolonging QTc in ICU admitted patients [35]. Nevertheless, the interaction between hydroxychloroquine and azithromycin, two medications with QTc prolongation effect coadministered in some COVID-19 patients, is graded as B interaction [36]. For B interactions, no intervention is needed according to the Lexi-Interact database but calculating the risk score of

QTc prolongation before administration of this combination to COVID-19 patients is a wisely measure.

Excessive inflammation, platelet activation, endothelial dysfunction, and stasis may lead to arterial and venous thrombotic disease in COVID-19 patients [37]. Drug interactions of common anticoagulants should be considered in these patients. In the current study, apixaban and rivaroxaban were administered to the patients. Among novel oral anticoagulants (NOACs), apixaban and rivaroxaban are substrates for both P-glycoprotein transporter and CYP3A4. Therefore, concomitant administration with inhibitors of CYP3A4 and P-glycoprotein transporter (e.g., lopinavir/ritonavir) should be avoided due to elevated serum concentration of apixaban and rivaroxaban and risk of bleeding [38].

Additionally, coadministration of antiplatelets or NSAIDs with anticoagulants may increase the risk of bleeding [39]. Because of underlying cardiovascular diseases in some COVID-19 patients, they may regularly use antiplatelet agents. NSAIDs may also be prescribed to relieve myalgia [40] or for their probable effect on SARS-CoV-2 (specifically indomethacin) [41]. Anticoagulants side effects should be monitored in COVID-19 patients receiving these combinations.

Administration of salmeterol or combination medications containing salmeterol may be indicated in COVID-19 patients with underlying chronic respiratory diseases. Lopinavir/ritonavir elevates serum concentration of salmeterol [42] and may predispose patients to cardiovascular adverse effects of beta2-agonists.

Another important interaction that may occur in COVID-19 male patients with older age is between tamsulosin and lopinavir/ritonavir. Although the adverse consequences of this interaction have not been evaluated in the clinical studies, this combination is contraindicated according to the tamsulosin drug label [43]. When the combination must be used, monitoring tamsulosin adverse effects (particularly orthostatic hypotension) is recommended.

Logistic regression analysis revealed that the occurrence of D and X pDDIs is significantly associated with two comorbidities (IHD and CRDs) and ICU admission. Patients with IHD or CRDs may receive the medications which interact with investigational drugs for COVID-19 especially protease inhibitors. We found other investigational medications (used for our patients) including hydroxychloroquine, ribavirin, remdesivir, favipiravir, interferon beta, or intravenous immunoglobulin do not have D or X interaction with commonly used medications for comorbidities. Therefore, these medicines are much safer than

protease inhibitors in terms of DDIs. We also found that critically ill patients are more prone to DDIs because they have complicated conditions and receive more medications.

Our study has some limitations. First, we could not find the evidence for the occurrence of side effects related to pDDIs in the patients' records. However, this may be related to the critical pandemic condition and time limitation for recording subjective and objective evidence for an actual DDI. This evidence can be collected through a prospective study in order to report actual DDIs. In addition, as a cross-sectional (descriptive-analytical) study, we found the potential risk factors of DDIs in COVID-19 patient. However, due to the limitation of this kind of studies, it should be cared not to make causal inferences [44]. Second, the software utilized by health-care practitioners to find DDIs cannot analyze individual genetic variation, which has an important effect on the occurrence and severity of DDIs [45]. The Lexi-Interact database also has this limitation. Third, some hospitals or countries may manage the patients differently. However, according to a systematic review, treatment protocols between countries vary slightly [46]. Therefore, our results can be extrapolated to the settings with similar prescribed medications.

Conclusions

Patients with COVID-19 exposed to many pDDIs that 18% of them were clinically important with the good and excellent levels of evidence. The interactions are more likely to happen in COVID-19 patients receiving medications with the potential of DDIs (protease inhibitors) and having comorbidity (IHD and CRDs). Choosing an alternative medication or adjusting the dosage of interacting drugs can improve patients' management by both providing essential medications and preventing adverse drug effects.

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Informed consent: Written informed consent by the patients was waived due to the retrospective nature of the investigation.

Ethical approval: The Ethical Review Board of the national research institute of tuberculosis and lung diseases approved the study protocol.

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