Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Meta-analysis on outcome-worsening comorbidities of COVID-19 and related potential drug-drug interactions

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ABSTRACT

Drug-drug interactions (DDI) potentially occurring between medications used in the course of COVID-19 infection and medications prescribed for the management of underlying comorbidities may cause adverse drug reactions (ADRs) contributing to worsening of the clinical outcome in affected patients. First, we conducted a meta-analysis to determine comorbidities observed in the course of COVID-19 disease associated with an increased risk of worsened clinical outcome from 24 published studies. In addition, the potential risk of DDI between medications used in the course of COVID-19 treatment in these studies and those for the management of observed comorbidities was evaluated for possible worsening of the clinical outcome. Our meta-analysis revealed an implication cardiometabolic syndrome (e.g. cardiovascular disease, cerebrovascular disease, hypertension, and diabetes), chronic kidney disease and chronic obstructive pulmonary disease as main co-morbidities associated with worsen the clinical outcomes including mortality (risk difference RD 0.12, 95 %-CI 0.05−0.19, p = 0.001), admission to ICU (RD 0.10, 95 %-CI 0.04−0.16, p = 0.001) and severe infection (RD 0.05, 95 %-CI 0.01−0.09, p = 0.01) in COVID-19 patients. Potential DDI on pharmacokinetic level were identified between the antiviral agents atazanavir and lopinavir/ritonavir and some drugs, used in the treatment of cardiovascular diseases such as antiarrhythmics and anti-coagulants possibly affecting the clinical outcome including cardiac injury or arrest because of QTc-time prolongation or bleeding. Concluding, DDI occurring in the course of anti-Covid-19 treatment and co-morbidities could lead to ADRs, increasing the risk of hospitalization, prolonged time to recovery or death on extreme cases. COVID-19 patients with cardiometabolic diseases, chronic kidney disease and chronic obstructive pulmonary disease should be subjected to particular carefully clinical monitoring of adverse events with a possibility of dose adjustment when necessary.

1. Introduction

The recent outbreak of the novel coronavirus officially known as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has progressed into global pandemic. Up to September 6, 2020 the World Health Organization (WHO) recorded 26,763,217 confirmed cases and 876,616 deaths in 216 countries worldwide [1]. An estimated 20–51 % of affected patients are reported to have at least one comorbidity [2,3]. These affected patients with underlying comorbidities may have a greater risk of poor clinical outcome including severity, mortality, and admission to ICU [4–6]. Again, it is expected that given the percentage of individuals with comorbidities affected by the COVID-19, the use of polypharmacy for treatment of existing chronic disease conditions might be a routine.

Since the inception of SARS-CoV-2 outbreak in the Chinese city of Wuhan in late 2019, several antiviral drugs and other medications currently utilized in clinics with known safety profile are repurposed in COVID-19 patients to reduce worsening of the symptoms [7,8]. On May 1, 2020, the US Food and Drug Administration (FDA) issued an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of hospitalized adults and children with severe COVID-19 based on clinical trial data. Nonetheless, some of these drugs are known to cause severe drug-drug interactions (DDI) such as hydroxychloroquine and azathioprine leading to increased risk of QTc-time prolongations [9]. With respect to co-morbidities in COVID-19 patients there is an additional potential risk of DDI between antiviral agents and multiple medications prescribed to treat their chronic disease conditions. It was shown that in northern Italy COVID-19 patients

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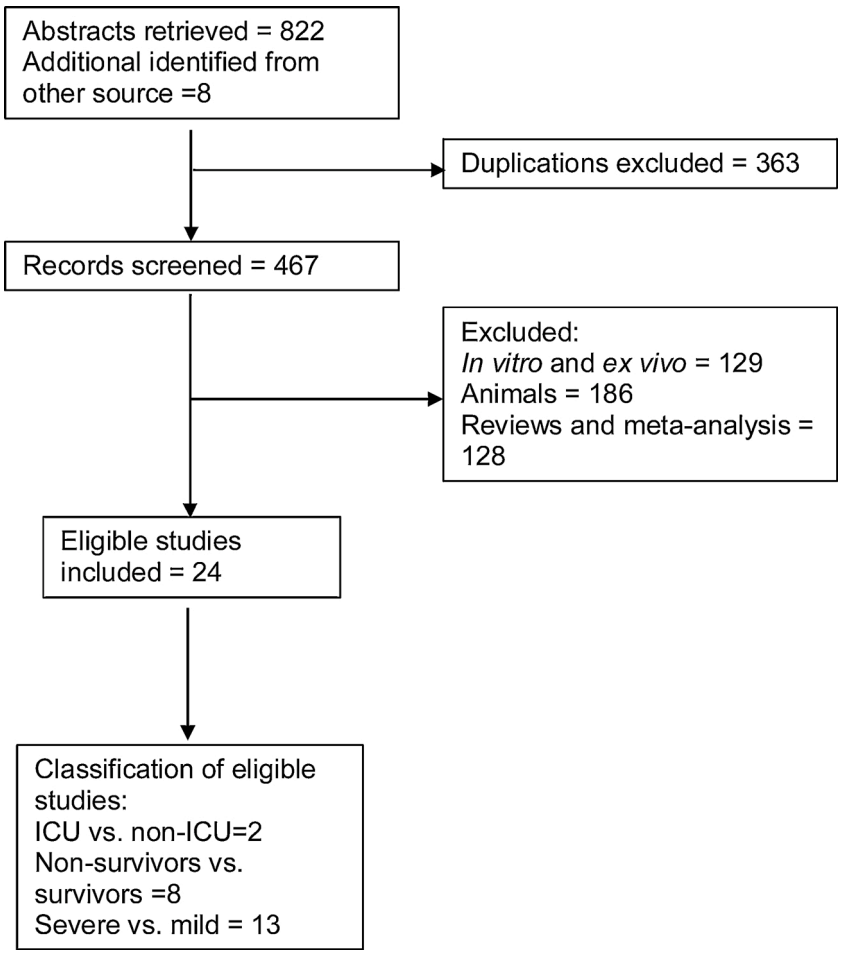


Fig. 1. Flow diagram indicating publications on clinical COVID-19 studies excluded and included in the meta-analysis.

experienced significant elevated plasma concentrations of direct oral anti-coagulants while on medications used in the course of COVID-19 [10]. Unfortunately, with the exception of hydroxychloroquine and QTc-time prolongation due to co-administration of other drugs, the issue of potential harmful DDI in COVID-19 comorbid patients seems to be of minor attention with a limited number of published studies currently available [11–15]. Also, of a public health concern is the use of self-medication being potentially harmful or without evidence of clinical benefit taking place particularly in low- and middle-income countries with restricted access to quality healthcare and where drug dispensing is less controlled in the communities [16,17]. We hypothesized that in addition to comorbidities, DDI may further worsen the clinical outcome of COVID-19 in these patients.

Herein, we first conducted a meta-analysis on COVID-19 clinical studies which characterized the epidemiological or clinical features of affected patients with comorbidities independent of pharmacological interventions. Secondly, the potential risk of DDI between drugs used in the course of COVID-19 and other medications prescribed for treatment of comorbidities were identified leading to potentially ADRs increasing the risk of poorer clinical outcome (e.g. hospitalization, prolonged time to recovery and death on extreme cases).

2. Methods

2.1. Search strategy and study criteria

Electronic databases of PubMed, Medline, Scopus and google scholar were searched for articles published before June 17, 2020 in English-language reporting on COVID-19. A combination of search terminologies ("COVID-19", "coronavirus", "nCOV", SARS-CoV-2") AND ("clinical characteristics") AND ("epidemiological features") AND ("chronic diseases") AND ("comorbidities") were used for the search. Additional studies were obtained by examining the references of selected articles. Selection criteria for the analysis focused exclusively on clinical studies characterizing the clinical or epidemiological features of COVID-19 patients. Only studies with confirmed SARS-CoV-2-RNA detection in respiratory specimen including nasopharyngeal swabs, bronchoalveolar lavage fluid, sputum, or bronchial aspiration as well as in plasma were included in the meta-analysis. Clinical signs of the infection such as fever, cough, myalgia, malaise, rhinorrhea, arthralgia, chest pain and dyspnea were also taken into consideration. Other clinical complications such as acute kidney and cardiac injuries were considered. We excluded studies conducted in children, pre-clinical models, case reports, letters, editorial commentaries, reviews, and meta-analysis.

2.2. Statistical analysis

The risk difference method was used to estimate weights of individual study outcome using the Mantel-Haenszel method with random-effect model in the R statistical software (version 3.4.2). The statistical heterogeneity between study outcomes were visualized using the forest plot and the inter-study heterogeneity estimated by calculating the τ^2, I^2 and H^2 statistics, and by computing Cochran's Q test statistics [18,19]. An I^2 values lower than 25 % was considered as low heterogeneity, values of 26–50 % indicated moderate heterogeneity and values greater than 50 % to indicate a high heterogeneity. A Cochran's Q test statistics with p-value of < 0.05 was an indication of statistical significance

Table 1
Clinical characteristics of COVID-19 patients included in 24 eligible studies.

Author (year)	Origin	Design	Age (years)	Number of Patients								
				All	CVD	CRV	CKD	CLD	Diabetes	Hypertension	Malignancy	COPD
Cao et al., 2019 [47]	China	NA	54	102	5 (5%)	6 (6%)	4 (4%)	2 (2%)	11 (11 %)	28 (28 %)	4 (4%)	10 (10 %)
Chen et al., 2020 [48]	China	RD	62	274	23 (8%)	NA	NA	NA	47 (17 %)	93 (34 %)	7 (3%)	18 (7%)
Deng et al., 2020 [49]	China	RD	NA	225	NA	NA	NA	NA	NA	NA	NA	NA
Feng et al., 2020 [50]	China	RD	53	476	38 (8%)	17 (4%)	NA	NA	49 (10 %)	113 (24 %)	12 (3%)	22 (5%)
Guan et al., 2020 [51]	China	PD	47	1099	27 (3%)	15 (1%)	8 (1%)	NA	81 (7%)	165 (15 %)	10 (1%)	12 (1%)
Huang et al., 2020 [2]	China	PD	49	41	6 (15 %)	NA	NA	1 (2%)	8 (20 %)	6 (15 %)	1 (2%)	1 (2%)
Huang et al., 2020 [52]	China	RD	44	202	NA	NA	NA	NA	19 (9%)	29 (14 %)	NA	NA
Itelman et al., 2020 [53]	Israel	RD	52	162	NA	NA	2 (1%)	NA	30 (19 %)	49 (30 %)	NA	2 (1%)
Javanian et al., 2020 [54]	Iran	RD	60	100	20 (20 %)	NA	12 (12 %)	NA	37 (37 %)	32 (32 %)	4 (4%)	12 (12 %)
Liu et al., 2020 [55]	China	RD	49	40	NA	NA	NA	NA	6 (15 %)	6 (15 %)	NA	NA
Shi et al., 2020 [56]	China	RD	63	671	60 (9%)	22 (3%)	28 (4%)	NA	97 (15 %)	199 (30 %)	23 (3%)	23 (3%)
Sun et al., 2020 [57]	China	RD	44	55	NA	NA	NA	NA	5 (9%)	8 (15 %)	NA	NA
Wan et al., 2020 [58]	China	RD	47	135	7 (5%)	NA	NA	2 (2%)	12 (9%)	13 (10 %)	4 (3%)	NA
Wang et al., 2020 [6]	China	RD	56	138	20 (15 %)	7 (5%)	4 (3%)	4 (3%)	14 (10 %)	43 (31 %)	7 (10 %)	4 (3%)
Wang et al 2020 [59]	China	RD	51	107	13 (12 %)	6 (6%)	3 (3%)	6 (6%)	11 (10 %)	26 (24 %)	NA	3 (3%)
Wu et al., 2020 [60]	China	RD	43	280	57 (20 %)	NA	3 (1%)	7 (3%)	NA	NA	5 (2%)	NA
Xie et al., 2020 [61]	China	RD	60	79	7 (9%)	NA	NA	NA	8 (10 %)	14 (18 %)	NA	NA
Xu et al., 2020 [62]	China	RD	41	62	NA	1 (2%)	1 (2%)	7 (11 %)	1 (2%)	5 (8%)	NA	1 (2%)
Xu et al., 2020 [63]	China	RD	46	703	35 (5%)	NA	10 (1%)	29 (4%)	64 (9%)	118 (17 %)	9 (1%)	13 (2%)
Yang et al., 2020 [4]	China	RD	59.7	52	5 (10 %)	7 (14 %)	NA	NA	9 (17 %)	NA	2 (4%)	4 (8%)
Zhang et al., 2020 [64]	China	RD	57	140	7 (5%)	NA	NA	NA	17 (12 %)	42 (30 %)	NA	2 (1%)
Zheng et al., 2020 [65]	China	RD	45	161	4 (3%)	4 (3%)	NA	4 (3%)	7 (4%)	22 (14 %)	NA	6 (4%)
Zhao et al., 2020 [66]	China	RD	46	91	NA	NA	1 (1%)	NA	3 (3%)	NA	3 (3%)	1 (1%)
Zhou et al., 2020 [67]	China	RD	56	191	15 (8%)	NA	2 (1%)	NA	36 (19 %)	58 (30 %)	2 (1%)	6 (3%)

*Median or average age (years. Abbreviations: cardiovascular disease (CVD), cerebrovascular disease (CRV), chronic kidney disease (CKD) and chronic liver disease. (CLD), retrospective design (RD), prospective design (PD), not specified (NS), not available (NA).

heterogeneity. The trim and fill method was used to determine hypothetical missing studies as evidence of publication bias when necessary (Supplementary Fig. 1).

2.3. Potential drug-drug interactions

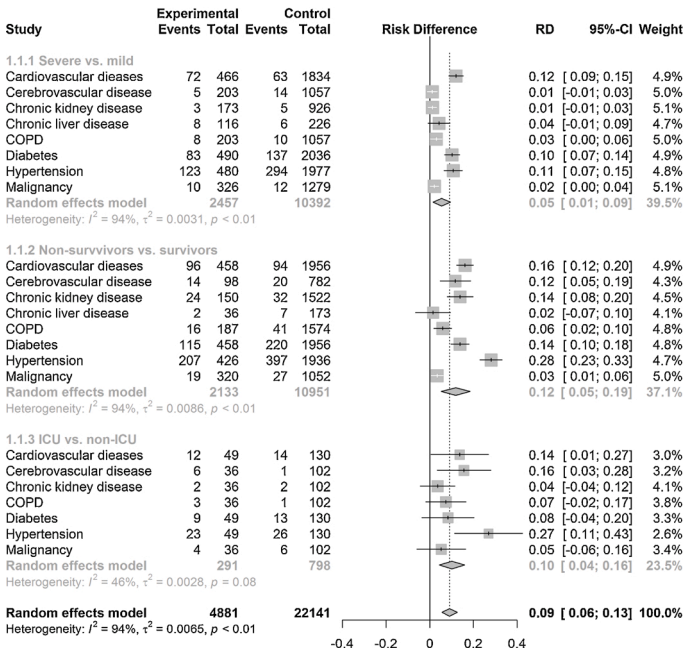
The data on drugs used in the course of COVID-19 and the primary indication were collected from www.ashp.org/COVID-19 as well as metabolizing enzymes involved in their biotransformation from www.drugbank.ca. The potential of drugs used in the course of COVID-19 infection reported in the included studies to interact with other drugs used for the management of comorbidities which could precipitate ADRs likely to further worsen clinical outcome of COVID-19 based on our meta-analysis was assessed using the www.covid19-druginteractions.org database. Here, potential DDIs are classified into four groups: (i) no clinically significant interaction expected; (ii) potential interaction likely to be of weak intensity with monitoring or dosage adjustment unlikely to be required; (iii) potential clinically significant interaction that may require close monitoring, alteration of drug dosage or timing of administration; and (iv) drugs should not be co-administered. We subsequently focused our analysis only on the latter. The clinical relevance of such DDI were risk ranked into five categories based on the quality of evidence as: (0) unlikely - no evidence of preclinical or clinically significant interaction, (1) very low - in vitro or animal studies, single case reports, parallel or crossover single dose pharmacokinetic (PK) study without area under plasma concentrations (AUCs), PK study in infected or healthy subjects, (2) low - multiple case reports, crossover or parallel steady state PK without AUCs, parallel or crossover single dose PK study with AUCs, metabolism study with probe substrates, observational PK in infected patients, (3) moderate - cross-over, parallel steady state PK study with AUCs and (4) high - data based on randomized, controlled interaction trial with clinical or validated surrogate endpoints.

The grading on quality of evidence of DDI was conducted for each medication prescribed for the treatment or management of comorbidities against individual COVID-19 therapies. Subsequently, the z-score was calculated and used to construct heatmaps in www. software. broadinstitute.org/morpheus.

3. Results

3.1. Study characteristics

A literature search was conducted to extract eligible studies for the meta-analysis. Of 467 records screened for eligibility, 24 prospective and retrospective case studies with a total of 5,586 COVID-19 affected patients were included in the meta-analysis (Fig. 1). Data on the underlying comorbidities was drawn from the reported clinical characterization of the affected patients. Comorbidities reported include cardiovascular diseases, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, malignancy, human immunodeficiency virus (HIV) and others. The mean age of the affected patients ranged from 41 years to 63 years (Table 1).



Drug class	Examples of drugs prone to DDIs
Antiarrhythmics	amiodarone, bepridil, disopyramide, dofetilide, flecainide, mexiletine, quinidine
Anticoagulants	apixaban, clopidogrel, dabigatran, rivaroxaban, ticagrelor
Antidiabetic	repaglinide
Bronchodilator	salmeterol
Statins	lovastatin, simvastatin
Angina pectoris	ranolazine
Heart failure	eplerenone, ivabradine
Pulmonary arterial hypertension	bosentan, *sildenafil
Hypertension	aliskiren, lercanidipine

Fig. 2. Meta-analysis of comorbidities in COVID-19 patients and typical related drugs. Cardiometabolic syndrome (cardiovascular disease, hypertension, and diabetes) was associated with worse clinical outcome of COVID-19 in affected patients. Drugs used for management or treatment of comorbidities: antihypertensives, antiarrhythmics, lipid lowering drugs (statins) listed could increase poor clinical outcome in comorbid patients by potential interaction with drugs used in the course of COVID-19. *indication for both pulmonary hypertension and erectile dysfunction.

3.2. Meta-analysis

Based on the 24 identified eligible studies, a meta-analysis was conducted to determine comorbidities which may be associated with an increased risk of clinical outcome in COVID-19 affected patients. For the meta-analysis, we separated the comorbidities based on non-survivors vs. survivors, ICU vs. non-ICU and severity vs. mild cases depending on the clinical presentations of signs and symptoms of the COVID-19 patients as reported by individual studies. In general, we observed poorer clinical outcome for COVID-19 patients with co-morbidities in ascending order of severe vs. mild (risk difference (RD) 0.05, 95 % CI 0.01 – 0.09, p = 0.01), ICU vs. non-ICU (RD 0.10, 95 % CI 0.04−0.16, p = 0.001), and non-survivors vs. survivors (RD 0.12, 95 % CI 0.05 – 0.19, p = 0.001) (Fig. 2). The analysis on non-survivors vs. survivors group showed hypertension, cardiovascular disease, diabetes, cerebrovascular disease, chronic kidney disease and malignancies were associated with significant increase in risk of death among COVID-19 patients. Other diseases including COPD and chronic liver disease had no impact on the risk of death among infected patients, for details see Fig. 2. For cases admitted to ICU, affected patients with cerebrovascular disease showed a high risk (RD 0.16, 95 % CI 0.03 – 0.28, p = 0.01) but the data was insufficient to strengthen the outcome (Fig. 2). Similarly, the analysis on severe vs. mild COVID-19 infection indicated that hypertension, diabetes, and COPD were associated with increase severity of infection in patients as depicted in Fig. 2. Cardiovascular disease was a borderline risk factor in severe COVID-19 patients. The meta-analyses on individual studies included in respective groups are shown in supplementary Figs. 2–4.

In subgroup analyses, low statistical heterogeneity was found in those (non-survivors vs. survivors) with chronic kidney disease (I^2 26.0, Q 5.39) and diabetes (I^2 21.0, Q 10.5), and high heterogeneity in patients with COPD (I^2 52.0, Q 8.37) and cardiovascular disease (I^2 70.0, Q 26.4). Patients (those in ICU vs. non-ICU) with diabetes (I^2 84.8 %, Q 6.56) and hypertension (I^2 83.1, Q 5.92) showed high heterogeneity. In addition, high heterogeneity was indicated in patients (those with severe vs mild) with diabetes (I^2 56.2, Q 22.82), hypertension (I^2 66.6, Q 27.0), and cardiovascular disease (I^2 90.4, Q 62.74) as shown in Table 2.

3.3. Potential drug-drug interactions

From the meta-analysis, comorbidities associated with increased risk of worsen clinical outcome in COVID-19 patients were cardiovascular disease, cerebrovascular disease, hypertension, diabetes, chronic kidney disease and chronic obstructive pulmonary disease. Further, several drugs have been used in different countries in the course of COVID-19 infection as reported in various studies included in the meta-analysis. Hence, we further used the www.covid19-druginteractions.org database to estimate the potential interaction risk of antiarrhythmics, antihypertensives, anticoagulants, antidiabetics, lipid lowering medications (statins), and bronchodilators with drugs used in the course of COVID-19 patients. A list of 41 drugs used in the course of COVID-19, their primary indication as well as main metabolizing enzymes are documented in Table 3. The use of hydroxychloroquine and lopinavir/ritonavir in COVID-19 was suspended or stopped in the WHO SOLIDARITY trial. According to the International Steering Committee interim trial report, hydroxychloroquine and lopinavir/ritonavir produced little or no decline in the mortality of hospitalized COVID-19 patients when compared to standard of care (www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19). However, these drugs are still used for the COVID-19 infection at some hospitals in other countries. Hence, both drugs were included in our DDI analysis.

According to the analysis, co-administration of some drugs used for the treatment or management of comorbidities together with atazanavir and lopinavir/ritonavir (used as therapies for COVID-19) could increase the risk of adverse outcome of COVID-19 patients by evidence of potential pharmacokinetic interactions. E.g. an increase in plasma exposure of antiarrhythmics (e.g. amiodarone, bepridil, disopyramide,

Table 2
Results of meta-analysis and subgroup analysis on comorbidities in COVID-19 patients.

Condition	Point estimate [95 % CI]	P value	Heterogeneity I^2 (%)	Q	T^2
Non-survivors vs survivors					
Cardiovascular disease	0.18 [0.1; 0.26]	<0.0001	70.0	26.41	0.010
Cerebrovascular disease	0.11 [0.04; 0.18]	0.001	–	0.13	–
Chronic kidney disease	0.11 [0.04; 0.17]	0.001	26.0	53.9	–
Chronic liver disease	0.01 [-0.07; 0.10]	0.72	–	0.23	–
COPD	0.05 [-0.01; 0.11]	0.10	52.0	8.37	–
Diabetes	0.14 [0.08; 0.19]	<00000.1	21.0	10.15	–
Hypertension	0.29 [0.23; 0.34]	<0.00001	–	6.78	0.010
Malignancy	0.04 [0.01; 0.06]	0.008	–	1.91	–
ICU vs non-ICU					
Cardiovascular disease	0.14 [0.01; 0.27]	0.004	–	0.01	–
Chronic kidney disease	0.04 [-0.02; 0.17]	0.38	–	–	–
COPD	0.07 [-0.02; 0.17]	0.12	–	–	–
Diabetes	0.01 [-0.33; 0.34]	0.98	84.8	6.56	0.050
Hypertension	0.20 [-0.16; 0.56]	0.28	83.1	5.92	0.060
Malignancy	0.05 [-0.06; 0.16]	0.36	–	–	–
Severe vs mild					
Cardiovascular disease	0.10 [0.00; 0.20]	0.05	90.4	62.74	0.015
Cerebrovascular disease	0.01 [-0.01; 0.03]	0.32	–	–	–
Chronic kidney disease	0.01 [-0.01; 0.03]	0.24	–	–	–
Chronic liver disease	0.03 [-0.02; 0.08]	0.19	–	0.04	–
COPD	0.03 [0.00; 0.06]	0.003	–	0.03	–
Diabetes	0.08 [0.02; 0.14]	0.002	56.2	22.82	0.004
Hypertension	0.10 [0.08; 0.20]	0.007	66.6	26.97	0.010
Malignancy	0.01 [0.00; 0.03]	0.13	–	2.61	–

*COPD = chronic obstructive pulmonary disease.

dofetilide, flecainide and quinidine), drugs prescribed for pulmonary hypertension (e.g. bosentan and sildenafil), angina pectoris (e.g. ranolazine), heart failure (e.g. eplerenone, ivabradine), erectile dysfunction (e.g. sildenafil), few anti-hypertensives (e.g. aliskiren and lercanidipine), antithrombotics and anticoagulants (e.g. ticagrelor and rivaroxaban), and statins (e.g. lovastatin and simvastatin) was detected due to a potential inhibition mainly of CYP3A4 by atazanavir or lopinavir/ritonavir (Fig. 3). Additionally, atazanavir and lopinavir/ritonavir may increase plasma concentrations of the anti-coagulant dabigatran by inhibiting the efflux drug transporter P-glycoprotein (P-gp). The HIV-protease inhibitor atazanavir was also shown before to inhibit CYP3A4, CYP2C8 and hepatic transporter OATP1B1 thereby increasing systemic exposure of antidiabetic drug repaglinide. The protease inhibitors lopinavir/ritonavir may also increase plasma exposure of the bronchodilator salmeterol via CYP3A4 inhibition. Azithromycin, chloroquine, or hydroxychloroquine used in the frame of COVID-19 treatment are prone to cause QTc-time prolongation in the presence of antiarrhythmics as a single agent or combined due to pharmacodynamic interactions. The summary of drugs used in the course of COVID-19 identified to cause clinically relevant interactions with other medications for the related co-morbidities are presented in Table 4.

We further estimated the potential interaction of combination therapies (e.g. azithromycin/nitazoxanide, hydroxychloroquine/azithromycin, and INF-β-1a/lopinavir-ritonavir/ribavirin) for COVID-19 because some of the included studies reported coadministration of these medications. In general, lack of evidence of clinically significant DDI was found. Potential interaction between other COVID-19 drugs (e.g. remdesvir, darunavir/cobistat, favipiravir, nitazoxanide, ribavirin, tocilizumab, sarilumab, IFN-β-1a, oseltamivir and anakinra) and co-medications prescribed for the treatment of existing comorbidities identified based on the meta-analysis were found to be of a low certainty.

4. Discussion

Comorbidities associated with poor clinical outcome of COVID-19 in affected patients are widely reported in other studies [20–22]. The results of our meta-analysis confirmed hypertension, cardiovascular disease, and diabetes being strongly associated with increased mortality and severe courses of COVID-19. Patients with cerebrovascular disease were more likely to be admitted to ICU or even die. Interestingly, in the set of studies included into the meta-analysis, chronic kidney disease and malignancies were associated with increasing the risk of mortality whilst COPD increases the severity of COVID-19 in affected patients. In general, patients with these underlying comorbidities have greater risk of upper respiratory tract infections and pneumonia because of dysfunctional innate and adaptive immune system [20,22].

Current treatment of COVID-19 primarily depends on supportive care, antiviral and immunomodulatory drugs. Given the distribution of population living with the comorbidities (hypertension, cardio-cerebrovascular, diabetes, chronic kidney disease), predominantly middle aged and elderly, polypharmacy and DDI might be apparent. Unfortunately, the potential risk of DDI is largely unknown since most studies on COVID-19 do not provide details on interaction between drugs used in the course of COVID-19 and co-medications used for the management of other comorbidities in these patients. The studies included in the meta-analysis indicated several medications used in the course of COVID-19 in infected patients with other underlying comorbidities. Hence, we evaluated the potential interaction of drugs for the treatment of these comorbidities with drugs for COVID-19 reported in studies included in the meta-analysis. Based on our findings, of a greater safety concern was prolonged cardiac repolarization and QT interval by pharmacokinetic interaction of atazanavir and lopinavir/ritonavir with some drugs, used in the treatment of cardiovascular diseases such as ivabradine in heart failure, ranolazine in symptomatic treatment of angina pectoris, the antiarrhythmics amiodarone disopyramide and quinidine or the formerly used calcium channel blocker bepridil (a drug with putative anti-viral properties) via inhibition of CYP3A4 which may further increase the risk of torsade de pointes (TdP) [23–25]. Consequences of such interaction may increase risk of hospitalization, prolonged time to recovery and finally sudden cardiac death in extreme cases. Other risk factors of QTc-time prolongation and TdP include hypokalemia and chronic heart failure. Furthermore, atazanavir and lopinavir/ritonavir could interact with antithrombotics and anticoagulants (e.g. ticagrelor, dabigatran and rivaroxaban) through CYP3A4 and P-glycoprotein to induce bleeding complication [10]. Interestingly, a recent retrospective study found the use of statins in hospitalized

Table 3
Drugs used in the course of COVID-19 disease, classification, primary indication and main metabolic pathways.

Drugs	Classification	Primary indication	Substrate of (enzyme/ transporter)[b]	Inhibitor of	Inducer of
ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs)	Renin angiotensin aldosterone system (RAAS) inhibitor	High blood pressure and heart failure	– CYP2C9	– –	– –
Alteplase	Plasmin activator	Acute ST elevation myocardial infarction (STEMI), pulmonary embolism	–	–	–
Anakinra	Disease modifying anti-rheumatic agent	RA	–	–	–
Ascorbic acid	Vitamin C	Vitamin C deficiency	–	–	–
Atazanavir	HIV protease inhibitors	HIV infection	CYP3A4	CYP3A4	–
Azithromycin	Macrolides	Multiple bacterial infections	–	–	–
Baloxavir	Antiviral	Influenza	–	–	–
Baricitinib	Disease-modifying anti-rheumatic agent	Moderate to severe RA	CYP3A4	–	–
Bevacizumab	IgG1 antibody	Various cancer types	–	–	–
Chloroquine phosphate	Antimalarial (4-aminoquinoline derivative)	Malaria	CYP2C8, CYP3A4	CYP2D6	–
Colchicine	Antigout agents	Gout	CYP3A4, P-gp	–	–
Darunavir/cobicistat	HIV protease inhibitors	HIV infection	CYP3A	–	–
Emapalumab	Anti-interferon gamma	hemophagocytic lymphohistiocytosis	–		
Famotidine	Histamine H_2 antagonists	Peptic ulcer disease, gastroesophageal reflux disease, Zollinger-Ellison syndrome	–		
Favipiravir	Antiviral	Influenza	Aldehyde oxidase	–	–
Fingolimod	Immunosuppressant	Multiple sclerosis	Sphingosine kinase, CYP4F2	–	–
HMG-CoA reductase inhibitors (statins)	Antilipemic agent	Reduce risk of heart attack or stroke	CYP3A4, CYP3A5	–	–
Hydroxychloroquine sulfate	Antimalarial (4-aminoquinoline derivative)	Malaria, auto-immune diseases (lupus, rheumatoid arthritis)	CYP3A4	CYP2D6	–
Inhaled prostacyclins (e.g. epoprostenol, iloprost)	Vasodilating agents	Pulmonary arterial hypertension	–	–	–
Interferon beta 1a	Interferon	Multiple sclerosis	–	–	–
Ivermectin	Anthelmintic	Multiple parasitic infections	P-gp	–	–
Lopinavir	HIV protease inhibitor	HIV infection	CYP3A	CYP3A4	–
Methylprednisolone	Corticosteroid	Multiple conditions	11beta-hydroxysteroid dehydrogenases and 20-keto-steroid reductases	–	–
N-acetylcysteine	Antioxidant	Acetaminophen overdose	–	–	–
Niclosamide	Anthelmintic	Tapeworm infestations	CYP1A2, UGT1A1	–	–
Nitazoxanide	Antiprotozoal	GIT infections	–	–	–
Nitric oxide (inhaled)	Vasodilating Agent	Neonatal respiratory failure	–	–	–
NSAIDS (e.g. ibuprofen, indomethacin)	Nonsteroidal anti-inflammatory agent	Pain, fever, inflammation	CYP2C8/9, CYP2C19, UGT2B7	–	–
Oseltamivir	Neuraminidase inhibitor	Influenza	Esterases	–	–
Peg-interferon alpha 2b	Interferon	Hepatitis C and melanoma	–	–	–
Remdesivir	Antiviral	*COVID-19	CYP2C8, CYP2D6, CYP3A4	–	–
Ribavirin		Hepatitis C	Adenosine kinase		
Ritonavir	HIV protease inhibitors	HIV infection	CYP3A/CYP2D6	CYP3A4, P-gp	–
Ruxolitinib	Antineoplastic Agents	Bone marrow disorders	CYP3A4	P-gp	–
Sarilumab	Disease modifying anti -rheumatic agent	Moderate to severe RA in adults	–	–	–
Sildenafil	PDE5 inhibitor	Erectile dysfunction, pulmonary arterial hypertension	CYP3A4/CYP2C9	–	–
Siltuximab	Monoclonal antibody	Multicentric Castleman's disease	–	–	–
Sirolimus	Immunosuppressive agent (mTOR inhibitor	Prevent rejection of kidney transplant	CYP3A4	–	–
Tocilizumab	Disease-modifying antirheumatic agent	Moderate to severe rheumatoid arthritis (RA) in adults, systemic juvenile idiopathic arthritis-SJIA, other rheumatological conditions	Proteolytic enzymes	–	–
Umifenovir	Antiviral	Influenza	CYP3A4, UGT1A9, UGT2B7	–	–

* FDA and EMA emergency use authorization.
[b] Metabolizing enzymes information collected from Drugbank and product information, drug list data obtained from https://www.ashp.org/COVID-19.

COVID-19 patients to be associated with a lower risk of all-cause mortality and a favorable recovery profile compared to the non-statin group [26]. However, with regards to DDI, statins (e.g. lovastatin and simvastatin) may induce myopathy as consequence of an elevated plasma concentration of these statins because of CYP3A4 inhibition by atazanavir and lopinavir/ritonavir. For example, the AUC of statins lovastatin and simvastatin increased in the presence of ritonavir by up to 20-fold [27–29]. Hence, the use of less DDI-proned statins should be preferred. In Asthma, plasma concentration of salmeterol could increase due to inhibition of CYP3A4 by lopinavir/ritonavir. Such combination may result in salmeterol related side-effects including QTc-time prolongation, palpitations, and tachycardia [28,30].

Adverse events detected in these patients while co-treatment with drugs used in the course of COVID-19 e.g. azithromycin, chloroquine, and hydroxychloroquine and anti-hypertensives are not based on pharmacokinetic interactions but on known risks of TdP by prolonged cardiac polarization and QT interval of such combinations [31–33]. Nonetheless, hydroxychloroquine and chloroquine are also known to be

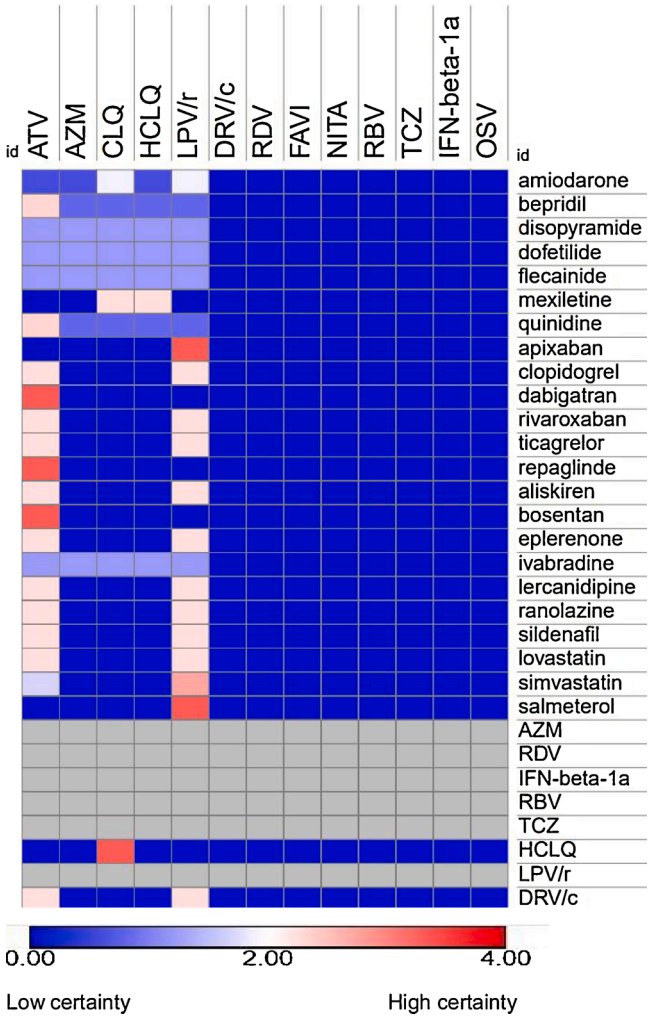


Fig. 3. Heatmap of potential DDI between drugs used in the course of COVID-19 and co-medications. The co-medications are putatively used for treatment of identified comorbidities (hypertension, cerebrovascular, cardiovascular, diabetes and COPD) based on results of the meta-analysis. Anti-viral drugs LPV/r and AZM interact with drugs prescribed for cardiometabolic syndrome. Potential interactions were predicting using www.covid19-druginteractions.org database. Abbreviations: atazanavir (ATV), azithromycin (AZM) darunavir/cobicistat (DRV/c), lopinavir/ritonavir (LPV/r), remdesivir/GS-5734 (RDV), favipiravir (FAVI), chloroquine (CLQ), hydroxychloroquine (HCLQ), nitazoxanide (NITA), ribavirin (RBV), tocilizumab (TCZ), interferon β-1a (IFN-β-1a) and oseltamivir (OSV).

inhibitors of cytochrome P450 2D6 (CYP2D6) hence contributing to an increased risk of TdP of the older antiarrhythmics flecainide and mexiletine [32–35]. Here, adjusting the recommended dose of hydroxychloroquine from 800 mg on day 1, followed by 400 mg daily for 4–7 days to a lower dose may be necessary to avoid potential adverse events (https://www.fda.gov/media/136537/download).

We additionally considered the potential interaction of combination therapies for COVID-19 azithromycin/nitazoxanide, hydroxychloroquine/azithromycin, tocilizumab/remdesivir, and triple combination (IFN-β-1a, lopinavir/ritonavir and ribavirin) used to tackle the pandemic. Studies have shown synergistic effects of these combinations therapies on inhibition of SARS-CoV-2 replication [36–39]. Generally, DDI of such combinations are uncertain due to lack of evidence. The azithromycin/hydroxychloroquine combination related TdP may occur as side effect of single or both drugs [31–33,37]. The antimalaria agent hydroxychloroquine is an inhibitor of P-glycoprotein [40]. However, pharmacokinetic interaction of azithromycin with hydroxychloroquine is unexpected because the former is not a sensitive substrate of P-glycoprotein [40,41]. Besides, hydroxychloroquine has long terminal elimination half-life (40–60 days) which may cause the risk of cardiac polarization and QT prolongation to persist even after discontinuation [34,42].

Prediction of DDI however could be hampered, since COVID-19 patients may experience phenoconversion whereby some genotypic extensive metabolizers transiently exhibit a decline in drug metabolizing enzyme activities comparable to that of poor metabolizers because of cytokine storm [43,44]. The problem of phenoconversion due to hyperactive immune system may increase the cardiac related side effects of drugs used in the course of COVID-19 (e.g. hydroxychloroquine) as consequence of prolonged plasma exposure [31,33,42]. Additionally, genetic polymorphism in drug metabolizing enzymes and transporters might worsen the side effects of drugs used for COVID-19 or in combination with other medications in individuals with defective genes.

On the other side, drugs used in the main regimens of hypertension, heart failure or diabetes did not show evidence of DDIs. In particular inhibitors of the renin angiotensin aldosterone system (RAAS) seem to be safe and concerns that the treatment with ACE-inhibitors could increase the risk of SARS-CoV-2 infections through elevation of the ACE-2 expression were not confirmed so far [45,46].

In conclusion, comorbidities including cardio-cerebrovascular diseases, hypertension, diabetes, and chronic kidney disease were associated with increased severity and mortality of COVID-19 in affected patients. DDI may be evident in these patients due to the use of polypharmacy as found in studies included in this meta-analysis. We have shown potential DDI particularly between antiretroviral drugs (atazanavir and lopinavir/ritonavir), and other drugs for treating comorbidity leading to TdP which might contribute to poorer clinical outcome (e.g. increased risk of hospitalization, prolonged time to recovery and death on extreme cases) in COVID-19 patients. This study cannot confirm whether the consequences of the DDI described change the expected course of COVID-19 since there are no clinical data available. To avoid adverse DDI, dose adjustment of drugs used in the course of COVID-19 prone to DDI or using an alternative drug for the management of related co-morbidity may be warranted to prevent risk of worsening clinical outcome. The findings of our study add to the knowledge on the potential risk of DDI in comorbid COVID-19 patients which is still an evolving area. It is worth noting that, this article is not intended to prevent the use of any medication but to outline the potential risk of specific DDIs which may further worsen the clinical outcome of COVID-19 patients with these comorbidities. Taken together, the choice of administration of medication in COVID-19 patients with comorbidities remains sole prerogative of the prescriber. However, we recommend that attention should be paid to symptoms that could indicate drug side effects in particular cardiac arrhythmia via DDI in these special population.

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Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.105250.

Table 4
Potential DDI between drugs used in the course of COVID-19 and medications for comorbidities.

Co-administered Drugs (CAD)	*CAD bioavailability (%)	*CAD Protein Binding (%)	Drug used the course of COVID-19	Mechanism of interaction	Example of interaction effect on AUC of CAD	Consequences of interaction	[b] Recommendations
Apixaban	50	92 - 94	Lopinavir/ritonavir	CYP3A4	Ketoconazole increases AUC of apixaban by 2-fold	Increased plasma concentration and bleeding	Avoid coadministration. Consider alternative anticoagulants
Amiodarone	35 - 65	96	Lopinavir/ritonavir	CYP3A4 inhibition	Indinavir increased amiodarone plasma concentration by 44 % via CYP3A4 inhibition	Increased amiodarone effects e.g. QTc-time prolongation, bradycardia, hypotension	Use with caution, monitor ECG, and adjust amiodarone
Bepridil	60	99	Atazanavir, lopinavir/ritonavir	–	–	Increased bepridil level effects. E.g. (QTc-time prolongation, hypotension	Do not co-administer
Bosentan	50	98	Atazanavir	–	Expected decreased atazanavir levels	Potential loss of antiviral activity	Do not co-administer bosentan with un-boosted atazanavir
Dabigatran	3 - 7	35	Atazanavir	P-gp inhibition	Dabigatran AUC increased by 110−127% via inhibition of intestinal P-gp by cobicistat	Increased risk of bleeding because of elevated dabigatran level	No dose adjustment if CrCL > 50 mL/min. avoid co-usage if CrCL < 50 mL/min
Eplerenone	69	50	Atazanavir, lopinavir/ritonavir	CYP3A4 inhibition	Ketoconazole as CYP3A4 inhibitor increases eplerenone AUC by 44 %	Increased plasma concentration, risk of hyperkalemia	Avoid co-administration
Lercanidipine	10	>98	Atazanavir, lopinavir/ritonavir	CYP3A4 inhibition	–	Increased plasma concentration	Monitor and adjust lercanidipine levels
Mexiletine	90	50 - 60	Chloroquine, hydroxychloroquine	CYP2D6 inhibition	–	Possible increased mexiletine effect e.g. Cardiac arrythmias	Do not co-administer
Quinidine	76 - 88	80 - 88	Atazanavir	CYP3A4 inhibition		Enhanced quinidine effects e.g. cardiac arrhythmia	Use with caution. Monitor for toxicity
Ranolazine	73	62	Atazanavir, lopinavir/ritonavir	CYP3A4 inhibition	Ketoconazole increased ranolazine AUC by 3.2-fold	QTc-time prolongation, cardiac arrythmias	Do not co-administer
Repaglinide	56	>98	Atazanavir	CYP3A4 inhibition	Clarithromycin increases repaglinide AUC by 40 %	Increase risk of hypoglycemia	Monitor repaglinide clinical effect and lower the dose if necessary
Salmeterol	–	96	Lopinavir/ritonavir	CYP3A4 inhibition	–	Potential increased salmeterol effects. E.g. QT prolongation, palpitations, sinus tachycardia	Do not co-administer
sildenafil	40	96	Lopinavir/ritonavir	CY3A4 inhibition	Clarithromycin and ciprofloxacin increased sildenafil AUC by 128 % and 110 %	Increased sildenafil effects. E.g. hypotension, priapism, visual changes	Start sildenafil at 25 mg QOD-QD; adjust dose, not recommended to exceed 25 mg in a 48 h period
Simvastatin	60	95	Lopinavir/ritonavir	CYP3A4 inhibition	Simvastatin acid exposure increased by 30-fold when co-administered with ritonavir/saquinavir	Increased plasma concentration effects (e.g. myopathy, rhabdomyolysis)	Do not co-administer. Alternative agents e.g. atorvastatin (low dose), pravastatin
Lovastatin	5	>95					

[*] Bioavailability and protein binding information collected from Drugbank and product information.
[b] Recommendations obtained from http://hivinsite.ucsf.edu/interactions.

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