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Review

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

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\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

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 \cite{WHO}. An estimated 20–51 \% of affected patients are reported to have at least one comorbidity \cite{WHO, Dehghan}. These affected patients with underlying comorbidities may have a greater risk of poor clinical outcome including severity, mortality, and admission to ICU \cite{WHO, Dehghan, Miller}. 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 \cite{Petersen, Kucharski}. 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 \cite{Petersen}. 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...
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 $I^2$, $H^2$ 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.
heterogeneity. The trim and fill method was used to determine hypo-
thesetical 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.dr
ugbank.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 treatment or management of comorbidities which could precipitate ADRs
likely to further worsen clinical outcome of COVID-19 based on our
administration; and (iv) drugs should not be co-administered. We sub-
that may require close monitoring, alteration of drug dosage or timing of
unlikely to be required; (iii) potential clinically significant interaction
no clinically significant interaction expected; (ii) potential interaction
of such DDI were risk ranked into five categories based on the quality of
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 comorbid-
ities 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 un-
derlying comorbidities was drawn from the reported clinical charac-
terization of the affected patients. Comorbidities reported include
cardiovascular diseases, cerebrovascular disease, chronic kidney disease (CKD) and chronic liver disease.

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 [52] | China | PD | 49 | 41 | 6 (15%) | NA | NA | 1 (2%) | 8 (20%) | 6 (15%) | 1 (2%) | 1 (2%) |
| Huang et al., 2020 [53] | China | RD | 44 | 202 | NA | NA | NA | NA | 19 (9%) | 29 (14%) | NA | NA |
| Isidori et al., 2020 | Israel | RD | 52 | 162 | NA | 2 (1%) | NA | 30 (19%) | 49 (30%) | NA | 2 (1%) |
| Javanian et al., 2020 | Iran | RD | 60 | 100 | 20 (20%) | NA | 12 (12%) | NA | 37 (37%) | 32 (32%) | 4 (4%) | 12 (12%) |
| Liu et al., 2020 [54] | China | RD | 49 | 40 | NA | NA | NA | 6 (15%) | 6 (15%) | NA | NA |
| Shi et al., 2020 [55] | China | RD | 63 | 671 | 60 (9%) | 22 (3%) | 28 (4%) | NA | 99 (15%) | 199 (30%) | 23 (3%) | 23 (3%) |
| Sun et al., 2020 [56] | China | RD | 44 | 55 | NA | NA | NA | NA | 5 (9%) | 8 (15%) | NA | NA |
| Wan et al., 2020 [57] | China | RD | 47 | 135 | 7 (5%) | NA | NA | 2 (2%) | 12 (9%) | 13 (10%) | 4 (3%) | NA |
| Wang et al., 2020 [58] | 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 [64] | China | RD | 59.7 | 52 | 5 (10%) | 7 (14%) | 7 (14%) | NA | 9 (17%) | NA | 2 (4%) | 4 (8%) |
| Zhang et al., 2020 [65] | China | RD | 57 | 140 | 7 (5%) | NA | NA | NA | 17 (12%) | 42 (30%) | NA | 2 (1%) |
| Zheng et al., 2020 [66] | China | RD | 45 | 161 | 4 (3%) | 4 (3%) | NA | 4 (3%) | 7 (4%) | 22 (14%) | NA | 6 (4%) |
| Zhao et al., 2020 [67] | China | RD | 46 | 91 | NA | 1 (1%) | NA | 3 (3%) | NA | 3 (3%) | 1 (1%) |
| Zhou et al., 2020 | China | RD | 57 | 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).*
insufficient to strengthen the outcome (Fig. 2). Similarly, the analysis on 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 increased risk of death among COVID-19 patients. Other risk factors in severe COVID-19 patients were cardiovascular disease, cerebrovascular disease, hypertension, diabetes, 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. Cardiovascular disease was a borderline risk factor in severe COVID-19 patients. The meta-analyses on individual 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 0.06–0.18, 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 increased 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 patients (those with severe vs. mild) with diabetes (I² 56.2, Q 22.82), hypertension (I² 66.6, Q 27.0), and cardiovascular disease (I² 90.4, Q 62.74) as shown in Table 2.

### 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 0.06–0.18, 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 increased 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 (I² 26.0, Q 5.39) and diabetes (I² 21.0, Q 10.5), and high heterogeneity in patients with COPD (I² 52.0, Q 8.37) and cardiovascular disease (I² 70.0, Q 26.4). Patients (those in ICU vs. non-ICU) with diabetes (I² 64.8 %, Q 6.56) and hypertension (I² 83.1, Q 5.92) showed high heterogeneity. In addition, high heterogeneity was indicated in patients (those with severe vs mild) with diabetes (I² 56.2, Q 22.82), hypertension (I² 66.6, Q 27.0), and cardiovascular disease (I² 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, anti-hypertensives, 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-ri tonavir-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,
CYP3A4, CYP2C8 and hepatic transporter OATP1B1 thereby increasing protease inhibitor atazanavir was also shown before to inhibit decrease plasma concentrations of the anti-coagulant dabigatran by atazanavir (Fig. 3). Additionally, atazanavir and lopinavir/ritonavir may in potential inhibition mainly of CYP3A4 by atazanavir or lopinavir/ritonavir could interact with antithrombotics and anticoagulants (e.g. sildenafil), few anti-hypertensives (e.g. aliskiren and lercanidipine), angina pectoris (e.g. ranolazine, lercanidipine, amiodarone disopyramide and QT interval by ibutilide, 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. remdesivir, darunavir/cockiat, 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 2

| Condition                  | Point estimate [95% CI] | P value | Heterogeneity |
|---------------------------|-------------------------|---------|---------------|
|                           |                         |         |               |
| 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]       | 0.11    |               |
| Hypertension              | 0.29 [0.23; 0.34]       | <0.00001| 21.0 10.15    |
| Malignancy                | 0.04 [0.01; 0.06]       | 0.008   | 1.91          |

**ICU vs non-ICU**

| Condition                  | Point estimate [95% CI] | P value | Heterogeneity |
|---------------------------|-------------------------|---------|---------------|
| 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     |
| Hypertension              | 0.20 [-0.16; 0.56]      | 0.28    | 83.1 5.92     |
| Malignancy                | 0.05 [-0.06; 0.16]      | 0.36    |               |

**Severe vs mild**

| Condition                  | Point estimate [95% CI] | P value | Heterogeneity |
|---------------------------|-------------------------|---------|---------------|
| Cardiovascular disease    | 0.10 [0.00; 0.20]       | 0.05    | 90.4 62.74    |
| Chronic kidney disease    | 0.01 [-0.01; 0.03]      | 0.32    |               |
| Chronic liver 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    |
| Hypertension              | 0.10 [0.08; 0.20]       | 0.007   | 66.6 26.97    |
| Malignancy                | 0.01 [0.00; 0.03]       | 0.13    | 2.61          |

*CDP = chronic obstructive pulmonary disease.*
COVID-19 patients should 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 a consequence of an elevated plasma concentration because of CYP3A4 inhibition by atazanavir. Such combination should be avoided due to the risk of prolonged cardiac repolarization and QT interval prolongation, palpitations, and tachycardia [28,30]. 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 [28,30]. Nonetheless, hydroxychloroquine and chloroquine are also known to be metabolized by CYP3A4 and CYP2D6. Therefore, the use of CYP3A4 inhibitors should be avoided. Other drug-induced liver injury (DILI) and drug-induced interstitial nephritis are also potential. The use of more DDI-proned statins should be avoided. In this context, 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 [28,30]. Nonetheless, hydroxychloroquine and chloroquine are also known to be metabolized by CYP3A4 and CYP2D6. Therefore, the use of CYP3A4 inhibitors should be avoided. Other drug-induced liver injury (DILI) and drug-induced interstitial nephritis are also potential.
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 an inhibitor of P-glycoprotein [40]. However, as side effect of single or both drugs [31].

Prediction of DDI however could be hampered, since COVID-19 patients may experience phenotypic shifts due to genotypic factors and 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 | Recommendations |
|-----------------------------|-------------------------|-------------------------|--------------------------------|--------------------------|---------------------------------------|----------------------------|------------------|
| Aripiprazole                | 50                      | 92 - 94                  | Lopinavir/ritonavir           | CYP3A4                   | Ketoconazole increases AUC of aripiprazole by 2-fold | Increased plasma concentration and bleeding | Avoid coadministration. |
| 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. |
| Bepiridil                   | 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                      | 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       | Glipizide AUC increased by 3.2-fold | Increased plasma concentration | Monitor and adjust lercanidipine levels. |
| Mexiletine                  | 90                      | 50 - 60                  | Atazanavir                   | CYP2D6 inhibition       | –                                    | Increased plasma concentration e.g. cardiac arrhythmias | Do not co-administer. |
| Quinidine                   | 76 - 88                 | 80 - 88                  | Atazanavir                   | CYP3A4 inhibition       | –                                    | Enhanced quinidine effects e.g. cardiac arrhythmias | Use with caution. Monitor for toxicity. |
| Ranolazine                  | 73                      | 62                      | Lopinavir/ritonavir           | CYP3A4 inhibition       | –                                    | QTC-time prolongation, cardiac arrhythmias | Do not co-administer. |
| Repaglinide                 | 56                      | >98                     | Atazanavir                   | CYP3A4 inhibition       | Glipizide AUC increased by 49% | Increased 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           | CYP3A4 inhibition       | Clarithromycin increases sildenafil AUC by 128% and 110 % | Increased sildenafil effects. E.g. hypotension, priapism, visual changes | Start sildenafil at 25 mg QOD; adjust dose, not recommended to exceed 25 mg in a 48 h period. |
| Simvastatin                 | 60                      | 95                      | –                            | CYP3A4 inhibition       | Simvastatin acid exposure increased by 3-fold when co-administered with ritonavir/saquinavir | Increased plasma concentration effects (e.g. myopathy, rhabdomyolysis) | Do not co-administer. |
| Lovastatin                  | 5                       | >95                     | Lopinavir/ritonavir           | CYP3A4 inhibition       | –                                    | Increased plasma concentration, risk of hyperkalemia | Do not co-administer. |

1 Bioavailability and protein binding information collected from Drugbank and product information.

2 Recommendations obtained from [http://hivinsite.ucsf.edu/interactions](http://hivinsite.ucsf.edu/interactions/).

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