Drug interactions in COVID-19 treatment. Systematic review

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The COVID-19 pandemic has driven the experimental, off-label treatments with co-administration of supportive therapies for many patients with severe infections and coexisting chronic conditions. This situation has inevitably led to polypharmacy, which is always related to a disproportionately large increase in drug-drug interaction and adverse drug effects probability. Immediate, difficult therapeutic decisions have taken priority, rendering drug interactions and adverse drug effects less important. Additionally, there has been a shortage of studies describing such interactions and guiding how to avoid them in clinical practice. Systematic review aimed to analyze and summarize the available information about clinically relevant drug-drug interactions observed between COVID-19 treatment and other drugs used in the care of individual patients.
To perform a systematic review, we searched PubMed and Embase databases. After data extraction, we checked drug-drug interactions with two independent interaction checkers: the COVID-19 Drug Interactions checker created by the University of Liverpool and the Drug Interactions Checker, powered by the American Society of Health-System Pharmacists, Cerner Multum, and IBM Watson Micromedex. According to our findings, chloroquine or hydroxychloroquine and lopinavir/ritonavir as a COVID-19 treatment carried the highest risk of interactions related to QT prolongation and cytochrome P450 inhibition. The other group most at risk of interactions involved patients taking immunosuppressants with the potential to prolong the QT interval and direct oral anticoagulants. In the case of immunosuppression therapy, one should expect increased blood levels of drugs and a higher risk of toxicity, co-administration of QT prolongation drugs involves the risk of life-threatening arrhythmias, and anticoagulant treatment requires paying attention to the increased risk of bleeding. Considering complex COVID-19 therapy, avoiding drug-drug interactions requires a multidisciplinary approach and up-to-date information about possible interactions.

Keywords: COVID-19 pharmacotherapy, drug interactions, drug safety, clinical pharmacy services.

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Introduction

Since December 2019, COVID-19 caused by severe acute respiratory syndrome coronavirus type 2 (SARS-COV-2) has rapidly spread worldwide. According to WHO data from 6 April 2022 (02:00 CEST), there have been till now 492,189,439 confirmed cases and 6,159,474 deaths due to COVID-19 [1]. Despite the high efficacy of vaccinations, reported as 66.1% for Johnson&Johnson one dose vaccine and 70.4–95.0% for two doses vaccines [2], and 64.7% of the world population receiving at least one dose of COVID-19 vaccination [3], there is still a need for the development of the specific treatments for the patients with severe symptoms.

The current COVID-19 treatment strategy is based on antiviral, anti-inflammatory, immunomodulators, and adjunctive therapies [4]. Among the recommended therapeutic options, chloroquine or hydroxychloroquine, lopinavir/ritonavir, and azithromycin were related to a higher risk of ADRs (adverse drug reactions) and DDIs (drug-drug interactions) [5, 6]. In the case of the off-label treatment by anti-malaria drugs and macrolides, the main problem cause QT prolongation by themselves and disproportionately more significant prolongation in combination or with another proarrhythmic drug co-administration [7]. Furthermore, according to PIs (protease inhibitors) like lopinavir/ritonavir, their interaction potential is associated with CYP (cytochrome) inhibition and decreases drugs' liver metabolism [6, 8].

Chronically ill patients are the most exposed group, experiencing interactions between COVID-19 therapeutics and other concomitant medications. Co-morbidities often require complex therapies, leading to problematic polypharmacy, one of DDIs and ADRs risk factors [9]. In the Iloanusi et al. study, polypharmacy was significantly related to an increased relative risk of a positive COVID-19 test result, deaths among male COVID-19 patients, AKI (acute kidney injury), and ADRs [10]. Additionally, a severe course of COVID-19 is almost synonymous with polypharmacy as it often relates to acute respiratory distress syndrome, acute respiratory failure, coagulopathy, septic shock, or cardiovascular complications treatment [4]. The critical condition of patients usually requires decisive actions in which drug interactions take a lesser priority. This systematic review is designed to draw attention to the problem of DDIs that can be avoided in the future treatment of patients with chronic illness and severe course of COVID-19.

The main aim of our review was to analyse the risk of DDIs between COVID-19 treatments and any other medications. In addition, we wanted to examine the scale of this problem in different groups of patients with chronic illness and summarise information about possible unsafe drug combinations.

Materials and methods

Systematic review

A systematic review was based on the newest PRISMA 2020 guideline [11]. The main goal of this study was to identify literature related to clinically relevant drug-drug interactions caused by COVID-19 treatment.

We searched articles published before 4 January 2022 in two different databases: PubMed and Embase. The research strategy for PubMed database was: ("drug interaction*"[tw] AND COVID--19[tw]) OR (COVID-19[Mesh] AND Drug Interactions[Mesh]) and for Embase database: ('drug interaction*:ti' AND 'COVID 19:ti') OR ('coronavirus disease 2019'/exp AND 'drug interaction'/exp). In both syntaxes, we used the same searching functions. We used a databases search engine filter to identify research conducted only on humans to narrow the search.

Inclusion criteria

The following types of full-text articles were selected for further analysis: randomised controlled trials, other controlled studies, observational studies, and case reports or case series. Furthermore, we considered only publications with drug-drug interactions caused by COVID-19 treatment with clinically important outcomes described in the articles. We excluded articles concerning potential drug-drug interactions without an accurate and sufficient clinical assessment of their consequences in patients included in the studies. Manuscripts in languages different from English were excluded.

To review titles and abstracts, we used the Rayyan software [12]. Two leading reviewers performed the first literature sift, reviewing titles and abstracts to identify relevant papers independently. After the agreement between the reviewers was achieved, the next step was to examine the full texts utilizing the same revision and decision scheme. All reviewing procedures are shown in a flow diagram (figure 1).

Data extraction

Following the agreement of all co-authors on papers included in this review, data extraction was performed on the selected documents. During another round of the revision, we collected data about the type of study, number of patients and

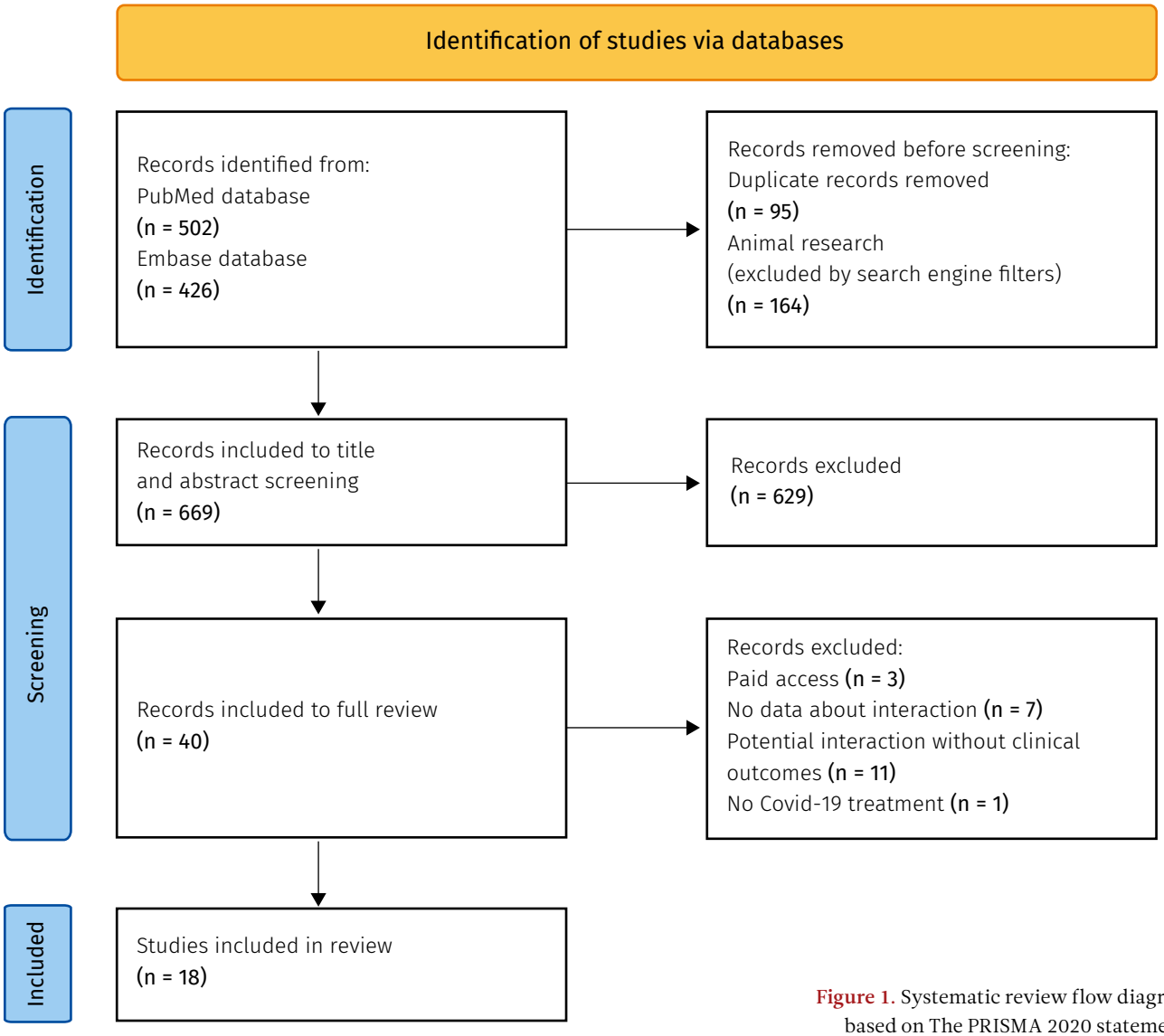

Figure 1. Systematic review flow diagram based on The PRISMA 2020 statement.

observed drug–drug interactions, drugs used for COVID-19 treatment, and classes and names of medicines that interact with them. When case reports or series were considered, we also collected information about the patient characteristics, such as age, weight, medications, and concomitant diseases. For better data readability Excel and Mendeley software were used.

Interaction checkers

To summarise information about drug interaction, we used two types of checkers. The first is dedicated to interpreting the interaction between COVID-19 treatment and another drug, created by the University of Liverpool [13]. The second is Drug Interactions Checker, designed and developed on www.drugs.com, powered by the American Society of Health-System Pharmacists, Cerner Multum, and IBM Watson Micromedex [14]. The abovementioned databases allowed for comparison of clinical interactions described in the articles with data derived from checkers such as the type of interaction, severity, risk ratio, and possessed information about management recommendations.

Results

Immunosuppressants

Immunosuppressant therapy after transplantation is associated with a significant risk ofpotentially dangerous DDIs, mainly due to CYP3A4 isoenzyme metabolism and interaction with P-glycoprotein, which lead to fluctuations in blood concentrations of the administrated drugs [15–17]. Clinically relevant interactions caused by CYP inhibitors may result in unpredicted, higher blood concentration levels of calcineurin and kinase mTOR inhibitors, manifested by symptoms of drug toxicity [15]. On the other hand, induction

of metabolisms threatens the risk of transplant rejection [16]. According to our review, during the COVID-19 treatment, PIs are the primary source of interactions (table 1).

Our systematic review found 9 out of 18 papers included in the analysis dealing with immunosuppressants DDIs, of which 6 were case reports. Among them, four articles described the usage of

Table 1. Clinically significant drug-drug interactions – immunosuppressants.

Group	Author/year	Type of paper	N	Administered drugs	COVID-19 treatment	Type of interaction	Clinical outcome	Risk by checkers
Immunosuppressants	Bartiromo et al. 2020 [18]	Case	1	Allopurinol, Methylprednisolone, Omeprazole, Ramipril, Tacrolimus†.	Ceftriaxone, Hydroxychloroquine, Lopinavir/Ritonavir† replaced after 2 days by Darunavir/Cobicistat.	Inhibition of CYP3A4 and P-glycoprotein	Increased trough the level of tacrolimus despite dose reduction	Major[1] NA[2]
	Meziyerh et al. 2020 [22]	Case	1	Everolimus†, NSAIDs, Prednisolone, Tramadol.	Cefuroxime, Chloroquine, Lopinavir/Ritonavir†.	Inhibition of CYP3A4 and P-glycoprotein	Increased trough the level of everolimus despite dose reduction (discontinued or changed to cyclosporine)	Major[1] NA[2]
	Ra et al. 2021 [23]	Case	1	Prednisolone, Sirolimus†.	Ceftriaxone, Lopinavir/Ritonavir†.	Inhibition of CYP3A4 and P-glycoprotein	Increased trough the level of sirolimus	Major[1] NA[2]
	Kim et al. 2020 [19]	Case	1	Mycophenolate mofetil was discontinued after starting Lopinavir/Ritonavir, Tacrolimus† discontinued after noticing an increasing trough level, Prednisolone changed after tacrolimus stopped to methylprednisolone.	Lopinavir/Ritonavir†	Inhibition of CYP3A4 and P-glycoprotein	Increased trough the level of tacrolimus despite discontinuation	Major[1] NA[2]
	Vongchaiudomchoke et al. 2021 [20]	Case	1	Diltiazem, Enalapril, Lamivudine, Mycophenolate sodium, Prednisolone, Tacrolimus†.	Azithromycin, Favipiravir, Hydroxychloroquine, Lopinavir/Ritonavir† discontinued after noticing an increased trough level of tacrolimus, Meropenem.	Inhibition of CYP3A4 and P-glycoprotein	Increased trough the level of tacrolimus despite dose reduction caused AKI	Major[1] NA[2]
Immunosuppressants	Thammathiwat et al. 2021 [21]	Case	1	Aciclovir, Co-trimoxazole, Glipizide, Losartan, Manidipine, Metoprolol, Mycophenolate mofetil was discontinued after starting COVID-19 treatment, Prednisolone, Simvastatin, Tacrolimus†.	Azithromycin, Ceftriaxone, Darunavir†, Favipiravir, Hydroxychloroquine, Immunoglobulin IVIg, Polymyxin B, Ritonavir†, Tocilizumab.	Inhibition of CYP3A4 and P-glycoprotein	Increased trough the level of tacrolimus despite dose reduction and finally stopped treatment	Major[1] NA[2]
	Martínez-López-de-Castro et al. 2021 [26]	Prospective single-centre study	1	Tacrolimus†	Hydroxychloroquine†	Inhibition P-glycoprotein	Increased trough the level of tacrolimus	NA[1] Potential[2]
	Miarons et al. 2021 [25]	Retrospective single-center study	106	Everolimus†, Sirolimus†, Tacrolimus†.	Lopinavir/Ritonavir†, Darunavir/Cobicistat†.	Inhibition of CYP3A4 and P-glycoprotein	Increased trough the level of everolimus, sirolimus and tacrolimus	Major[1] NA[2]
	Saez-Giménez et al.[24]	Retrospective multi-center study	10	Tacrolimus†	Lopinavir/Ritonavir†	Inhibition CYP3A4 and P-glycoprotein	Increased trough the level of tacrolimus despite dose reduction caused AKI	Major[1] NA[2]

† drug-drug interaction
[1] risk by Drugs.com interaction checker[14]
[2] risk by Liverpool COVID-19 Interactions checker[13]
NA – not available

tacrolimus, one sirolimus, one everolimus, and their subsequent interactions. The first case report described a 36-year-old woman following kidney transplantation (KT) treated with tacrolimus 5 mg/day and prednisolone 4 mg a day. Based on the COVID-19 diagnosis, physicians started treatment with lopinavir/ritonavir 400 mg/100 mg a day, hydroxychloroquine 200 mg/day, and ceftriaxone 2 g daily, and reduced the dosage of tacrolimus to 3 mg/day. On 2nd day of antiviral treatment, lopinavir/ritonavir was replaced by darunavir/cobicistat due to nausea and diarrhea. The patient reported intermittent abdominal pain, nausea, and vomiting on day 4. Tacrolimus trough level on that day was 90.5 ng/mL. Physicians discontinued antivirals and tacrolimus therapy and continued to monitor immunosuppressant levels. Two weeks after the hospital discharge (about 19 days after tacrolimus discontinuation), the tacrolimus level still was elevated up to 15 µg/mL [18]. The second case report described a 36-year-old man taking 2 mg of tacrolimus a day, 500 mg of mycophenolate mofetil (MFF) twice a day, and 10 mg/day of prednisolone following KT. As the Sars-CoV-2 virus was detected, physicians started lopinavir/ritonavir (400 mg/100 mg a day) and discontinued MFF. Due to an elevated level of tacrolimus (16 ng/mL), they decided to stop it and change 10 mg of prednisolone to 30 mg of methylprednisolone per day. A drop down to the therapeutic level of tacrolimus was achieved after ten days since the discontinuation of such treatment [19]. The third article reported a 39-year-old kidney recipient male on 2 mg/day tacrolimus, 720 mg/day mycophenolate sodium, and 2.5 mg/day prednisolone immunotherapy. Due to the COVID-19 diagnosis, the patient was started on hydroxychloroquine (1.200 mg/day), favipiravir (1.600 mg/day), and lopinavir/ritonavir (800 mg/400 mg a day) administration with concurrent 50% dosage reduction of tacrolimus, discontinuation of mycophenolate sodium, and increase of the prednisolone dose (15 mg/day). Despite the lower tacrolimus regime, the 10th-day trough level was still elevated up to 66.3 ng/mL, contributing to acute kidney injury and the decision to discontinue lopinavir/ritonavir treatment [20]. The fourth case was regarding a 58-year-old male with a transplanted kidney. Initial immunosuppressive therapy was based on 2.5 mg/day tacrolimus, 2 g/day MFF, and prednisolone of 2.5 mg a day. The antiviral treatment was started after a positive diagnosis of COVID-19. Physicians commenced favipiravir, darunavir/ritonavir, azithromycin, and hydroxychloroquine, followed by the reduction of tacrolimus dosage by half and discontinuation of MFF therapy. On the second day, tacrolimus, MFF, and the current antiviral therapy were stopped, except for favipiravir, as tacrolimus trough level was 28.9 ng/mL. For the immunotherapy, the prednisolone dosage was increased to 15 mg daily. Continued COVID-19 treatment was based on favipiravir, intravenous immunoglobulins (IVIG), tocilizumab, and antibiotic prophylaxis [21]. The following report presented a 35-year-old male on dual immunosuppressive therapy with 3 mg/day everolimus and 7.5 mg prednisolone after KT. Due to confirmed Sars-Cov-2 diagnosis, she was treated with 300 mg/day (after 600 mg loading) chloroquine and 400 mg/100 mg lopinavir/ritonavir daily. Physicians decided to reduce the everolimus dose to 2 mg a day, considering possible drug interaction. After two days, despite a lower dose, the everolimus level was 31.1 µg/mL. Therefore, on the same day, physicians stopped everolimus therapy completely. Everolimus concentration decreased below detection level after 22 days, and since then, cyclosporine was administered [22]. The last case report is also about a man with KT at 59 years of age. His immunosuppression regime included sirolimus (6 mg a day) and prednisolone (5 mg a day). On the day of COVID-19 diagnosis, 400 mg/100 mg a day of lopinavir/ritonavir and 2 g daily ceftriaxone was prescribed. On the fifth day, a laboratory test revealed a significant increase in AST and ALT levels; furthermore, sirolimus concentration measured the next day achieved 122.9 ng/mL. The authors mentioned that sirolimus trough level might cause drug-induced hepatitis, which was the reason to stop lopinavir/ritonavir treatment [23].

In a multicenter retrospective study of 44 adult lung transplant patients [24], the clinically significant interaction between lopinavir/ritonavir and tacrolimus was described. In 10 out of 14 patients (71.4%) receiving lopinavir/ritonavir therapy, the plasma levels of tacrolimus increased above the upper therapeutic limit, even though the tacrolimus dose was decreased or even the treatment was stopped. Furthermore, a high level of tacrolimus contributed to the increased risk of AKI – in 60% of patients with AKI high level of tacrolimus (> 15 ng/mL) was noted. Ten patients treated with lopinavir/ritonavir related to treatment AKI were diagnosed (mean eGFR 16 mL/min/m^2), and tacrolimus levels in this subgroup had a mean peak value of 28.5 (5.8–60) ng/mL. Also, due to the difficulties in dose adjustment of tacrolimus related to lopinavir/ritonavir therapy, subtherapeutic or undetectable levels of tacrolimus were observed in one patient.

In a cohort study by Miarons et al. [25], 46 transplant recipients treated for COVID-19 were included and compared to the control of 166 non-transplant COVID-19 patients (selected from

586 based on probabilistic matching taking into demographic characteristics). One of the outcomes reported was DDIs, i.e., all confirmed drug interactions and therapy modifications secondary to them. Also, all treatments were analyzed for potential drug interactions using online software for DDI checking. The data were analyzed 28 days after admission to the hospital. The total number of detected interactions was 106 in 42 (91.3%) transplant patients. Tacrolimus was the most frequent immunosuppressant associated with drug interactions (61.3% of all DDIs), whereas among anti-SARS-CoV-2-drugs involved in DDIs, the main was lopinavir (42.4% of all DDIs). Mainly, the tacrolimus was either discontinued (61,1% of patients) or the dose was reduced (50% of patients). However, the opposite effect – the need to increase tacrolimus doses/frequency was also reported (4 patients).

A retrospective cohort study by Martínez-López-de-Castro et al. mentioned two from 350 patients with DDI between hydroxychloroquine and tacrolimus. The cohort consisted of adult patients admitted to the hospital between 2 March and 8 May 2020 diagnosed with COVID-19, treated with hydroxychloroquine, lopinavir/ritonavir, interferon beta, or tocilizumab with at least one observed DDI between COVID-19 treatment and other administered drugs. Unfortunately, clinical outcomes were measured only in one of them and were manifested by higher tacrolimus blood levels [26].

To conclude, the risk of DDIs in transplant patients treated for COVID-19 is high and may result in adverse reactions and difficulties in establishing optimal immunosuppressant treatment. Moreover, the total risk of complications related to DDI, especially the most severe, like transplant rejection, which might have resulted from underdosing of immunosuppressant drugs, is difficult to assess because it needs a longer follow-up period. This is mentioned as one of the limitations in the study by Miarons et al. [25], where the analysis was made based of 28 days of observation.

QT-prolongation drugs

DDI leading to the risk of QT-prolongation represents the interactions that can lead to serious adverse cardiac events, i.e., Torsade de Pointes type arrhythmias and sudden cardiac death. Many drugs from different pharmacological groups have been linked with QT-prolongation risks, such as hydroxychloroquine (HCQ) used in COVID-19 treatment [27]. Although protease inhibitors (PIs) are potentially contributing to this interaction, the adverse event risk seems to be more related to patient-specific risk factors [28]. A summary of included papers is showed in table 2.

In the case report by Suyan Zu et al. [29], we found two similar cases of DDIs between chloroquine, umifenovir, and lopinavir/ritonavir treatment during a COVID-19 therapy. A first case was reported on a 56-year-old woman, treated with lopinavir/ritonavir (400 mg/100 mg twice a day), umifenovir (0,2 mg three times a day), and chloroquine (0.25 mg twice a day) commenced on day 9. The following day, QT interval prolongation to 482ms with a concurrent potassium level of 3,6 mmol/L was revealed. Therefore, physicians decided to discontinue lopinavir/ritonavir and

Table 2. Clinically significant drug-drug interactions – QT prolongation drugs.

Group	Author/year	Type of paper	N	Administered drugs	COVID-19 treatment	Type of interaction	Clinical outcome	Risk by checkers
QT-prolongation drugs	Koh et al. 2021 [31]	Retrospective study	13	ND	Hydroxychloroquine† Lopinavir/ritonavir†	2 drugs disproportionate increase QT	QT prolongation	Major[1] Potential[2]
			11	ND	Hydroxychloroquine† Atazanavir/ritonavir†	2 drugs disproportionate increase QT	QT prolongation	Moderate[1] Potential[2]
	Suyan Zu et al. 2020 [29]	Case	1	Pantoprazole, Methylprednisolone.	Chloroquine† Lopinavir/ritonavir† Umifenovir†	3 drugs disproportionate increase QT, inhibition CYP3A4	QT prolongation, Increased levels of umifenovir	Major[1] Potential[2]
			1	Pantoprazole	Chloroquine† Lopinavir/ritonavir† Umifenovir†	3 drugs disproportionate increase QT, Inhibition CYP3A4	QT prolongation Increased levels of umifenovir	Major[1] Potential[2]
	Anmella et al. 2020 [30]	Case	1	Venlafaxine†, Vortioxetine, Trazodone.	Lopinavir/ritonavir†, Hydroxychloroquine†, Azithromycin†.	4 drugs disproportionate increase QT	QT prolongation	Major[1] Do not coadminister[2]

† drug-drug interaction
[1] risk by Drugs.com interaction checker [14]
[2] risk by Liverpool COVID-19 Interactions checker [13]
ND – no data

start potassium supplementation. After five days, a QT interval decreased to an acceptable 410 ms, and a potassium level increased to 5.0 mmol/L. In the second case of the 56-year-old woman, chloroquine was started on the 8th day of antiviral therapy. On the same day, physicians measured a QT interval of 460 ms and decided to stop lopinavir/ritonavir treatment. Due to relative hypopotassemia (3.8 mmol/L), physicians agreed to start potassium supplementation. The acceptable length of QT interval (422 ms) was revealed after three days since lopinavir/ritonavir therapy was discontinued. In both cases, incidents of prolongation of QT intervals could be explained differently. One of them is a DDIs between lopinavir/ritonavir as a CYP3A4 inhibitor of umifenovir metabolism, which causes the manifestation of toxic effects and QT interval lengthening. On the other hand, lopinavir/ritonavir may cause fluctuation in potassium levels by interfering with potassium channels, therefore leading to changes in QT interval length.

Anmella et al. focused on problems with psychiatric therapy modifications due to COVID-19 treatment [30]. One of four cases described a 68-year-old woman with a diagnosis of depression and anxiety treated with venlafaxine (225 mg a day), vortioxetine (10 mg a day), and trazodone (50 mg daily). Due to the COVID-19 diagnosis requiring treatment, physicians started lopinavir/ritonavir (400 mg/100 mg daily), azithromycin (250 mg/day), and hydroxychloroquine (400 mg/24h), deciding to maintain antidepressive treatment with venlafaxine alone. However, on the second day, they observed QT prolongation (443 ms), which led to the withholding of venlafaxine treatment, which triggered insomnia, increased anxiety, and confusion. After psychiatric consultation, the decision was to return to previous antipsychotic therapy with a reduced dosage of venlafaxine to 150 mg/day with ECG monitoring. No further QT prolongation was observed.

Our systematic review selected a retrospective study examining QT-prolongation associated with HCQ and PIs, including 446 SARS-CoV-2 RT-PCR-positive patients taking HCQ and PIs, either concurrently or separately [31]. Other concomitant drugs leading to the risk of QT-prolongation were also considered. QT-prolongation was noticed in 28 patients (6.3%), with a proportion of the events for the HCQ-only, PI-only, and HCQ-PI combination groups of 2/219, 2/9, and 24/218, respectively. Multivariate analysis showed that concomitant administration of HCQ and PI led to five times higher odds of QT-prolongation when compared to the HCQ-only group (OR 5.2, 95% CI, 1.11–24.49, p = 0.036). Additionally, in the HCQ-PI group, administration of other pro-QT drugs resulted in further four times increase in odds of QT-prolongation (3.8; 95% CI, 1.53–9.73; p = 0.004). The patient's health status was also a significant factor contributing to the risk of QT-prolongation. The presence of SIRS (systemic inflammatory response syndrome) caused four times higher odds of QT-prolongation (OR 4.3; 95% CI, 1.66–11.06; p = 0,003). From the onset of HCQ or/and PI therapy, the average time to develop QT-prolongation was six days. Authors reported eight deaths in the study, of which four patients developed QT-prolongation. However, the causes of death were not linked to cardiac complications. In addition, there weren't any cases of malignant arrhythmias such as "torsade de pointes" reported in this group of patients.

In a retrospective cohort study by Martinez-Lopez-de-Castro et al. [26] about drug-drug interactions in the first wave of COVID-19 treatment, 218 of 350 patients (62.3%) experienced at least one potential DDI. Of the total 598 pDDI (potential drug-drug interaction), 38 (6.3%) were classified as not recommended combinations of drugs. The most significant pDDIs were related to HCQ and lopinavir/ritonavir. In the group of patients with cardiac adverse effects who had two ECGs (at the time of admission and following the start of COVID-19 treatment), 5.7% of them experienced significant QT-prolongation. All QT-prolongations were deemed a possible result of pDDI, and the median number of potential interactions in patients with QTc interval alteration was 2.0 (interquartile range: 1–7). However, in this study, the risk of QT-prolongation has not been assessed as well as it has not been examined if it was linked to any specific drug or drug combination. The risk of fatal complications was not increased due to QT-prolongation, with the risk of pDDI assessed throughout the treatment and concomitant discontinuation of the potential cardiotoxic therapy if needed. The role of hospital pharmacists involved in this study may have contributed to the reduced number of pDDI and severe clinical complications.

In conclusion, concomitant administration of drugs linked to QT-prolongation increases the risk of clinical events, and continuous ECG monitoring may prevent fatal complications of potentially cardiotoxic drugs.

Anticoagulant drugs

We found one case report by Launay et al. [32] about an 82-year-old man with COVID-19 and anticoagulant therapy (apixaban 5 mg twice a day). During treatment selection, clinicians cooperated with the consultant pharmacologist, who

suggested a possible interaction between apixaban and planned therapy with lopinavir/ritonavir. Due to CYP3A4 apixaban metabolism and P-gp (p-glycoprotein) elimination, ritonavir as a P-gp inhibitor could increase its anticoagulant activity, as previously described in the literature. Based on such available information, physicians decided to change anticoagulant treatment after 24 h washout to enoxaparin and start lopinavir/ritonavir. Despite that, due to the cumulative effect of metabolism inhibition, acute kidney injury caused by COVID-19, and the direct impact of inflammation, the apixaban half-life increased from standard 12 hours to 54 hours (about 450% elongation).

In a retrospective study by Testa S. et al. [33], authors screened 1039 patients with COVID-19 regarding direct oral anticoagulant treatment (DOAC). Thirty-two patients on antiviral therapy with DOACs were included in the study. In 20 of them, based on a decision of the attending physician, the prescribed drugs needed discontinuation. Due to that, the authors decided to include only 12 remaining patients in the analysis. In these 12 patients, plasma levels of DOAC were measured during their stay in the hospital and compared with the pre-hospitalization levels. An average 6.14 times increase in C-through DOAC concentration was noted. In addition to antiviral (Lopinavir, Darunavir, Ritonavir), all the patients had concomitant administration of hydroxychloroquine and azithromycin or levofloxacin.

In summary, anticoagulant CYP3A4 metabolism represents the main reason for interaction with COVID-19 treatment. On the other hand, cyclooxygenases inhibition cause hard to predict an increase in DOAC blood levels and prevent toxic effects. A summary description of DOAC DDIs found in our research presents in table 3.

Miscellaneous

The case report by Domingo-Chiva et al. [34] authors mentioned the possible interaction of rocuronium and lopinavir/ritonavir. In their study, a 54-year-old obese woman with COVID-19 disease was treated with lopinavir/ritonavir (400 mg/100 mg daily) for ten days and dexamethasone 20 mg/day for 5 10 mg/day for five next days. The patient required mechanical ventilation, provided by an anaesthetic ventilator due to a lack of ICU ventilators. To resolve the patient-respirator asynchrony, physicians administered midazolam-fentanyl first and then propofol-remifentanil, as per the patient's clinical condition. Additionally, continuous infusion of non-depolarising neuromuscular blocking agents was also required, with cisatracurium as a first-choice drug. On the 5th day, a different muscle relaxant – rocuronium, was prescribed and administered due to shortages of cisatracurium. Unfortunately, cisatracurium was available only four days later, and muscle relaxants were switched back. Due to clinical improvement, physicians decided to wean off mechanical ventilation, although observed irregular spontaneous respiratory patterns necessitated recommencement of the light sedation. After 24 hours, following a sedation hold patient was extubated. Despite rocuronium discontinuation for eight days, the patient displayed significant muscle weakness and presented low values on EMG. Strength and regular respiratory pattern were

Table 3. Clinically significant drug-drug interactions – anticoagulants.

Group	Author/year	Type of paper	N	Administered drugs	COVID-19 treatment	Type of interaction	Clinical outcome	Risk by checkers
Anticoagulants	Launay et al. 2021 [32]	Case	1	Apixaban† changed right before lopinavir/ritonavir therapy to enoxaparin	Lopinavir/ritonavir†	Inhibition of CYP3A4 and P-glycoprotein	Increased the level of apixaban despite discontinuation	Major[1] NA[2]
	Testa et al. 2020 [33]	Retrospective study	3	Apixaban†	Lopinavir/ritonavir†	Inhibition of CYP3A4 and P-glycoprotein	Increased the level of apixaban	Major[1] NA[2]
			2	Apixaban†	Darunavir/ritonavir†	Inhibition of CYP3A4 and P-glycoprotein	Increased the level of apixaban	Major[1] NA[2]
			3	Rivaroxaban†	Lopinavir/ritonavir†	Inhibition of CYP3A4 and P-glycoprotein	Increased the level of rivaroxaban	Major[1] NA[2]
			2	Edoxaban†	Darunavir/ritonavir†	Inhibition of CYP3A4 and P-glycoprotein	Increased the level of edoxaban	Major[1] NA[2]
			1	Edoxaban†	Lopinavir/ritonavir†	Inhibition of CYP3A4 and P-glycoprotein	Increased the level of edoxaban	Major[1] NA[2]
			1	Dabigatran†	Lopinavir/ritonavir†	Inhibition P-glycoprotein	Increased the level of dabigatran	Moderater[1] NA[2]

† drug-drug interaction
[1] risk by Drugs.com interaction checker [14]
[2] risk by Liverpool COVID-19 Interactions checker [13]
NA – not available

Table 4. Clinically significant drug–drug interactions – miscellaneous.

Group	Author/year	Type of paper	N	Administered drugs	COVID–19 treatment	Type of interaction	Clinical outcome	Risk by checkers
Miscellaneous	Domingo-Chiva et al. 2020 [34]	Case	1	Midazolam, Fentanil, Propofol, Remifentanil, Cisatracurium, Rocuronium†, others not mentioned.	Lopinavir/ritonavir†, Dexamethasone.	Inhibition CYP3A4	Prolonged curarization	No interaction[1] NA[2]
	Leegwate et al. 2021 [35]	Case	1	Enalapril, Amlodipine, Simvastatin, Amiodarone†.	Hydroxychloroquine†, Remdesivir†.	Inhibition of P–glycoprotein on hepatocyte membrane	Increase hepatotoxic effects of remdesivir	Moderate[1] No interaction[2]
	Sönmez Güngör et al. 2021 [36]	Original study	1	Risperidone†	Hydroxychloroquine†	Inhibition CYP2D6	Mild constipation	NA[1] Potential[2]
			1	Haloperidol†, Lithium†.	Hydroxychloroquine†	3 drugs disproportionate increase QT	Mild sinus bradycardia	Major[1] Do not coadminister[2]
			1	Olanzapine†, Haloperidol†, Valproates,	Hydroxychloroquine†, Ceftriaxone.	Possible inhibition of CYP2D6 and increased level of olanzapine and haloperidol	Mild elevation in ALT levels	NA[1] NA[2]
			1	Olanzapine†, Valproates, Benzodiazepines.	Hydroxychloroquine†	Possible inhibition of CYP2D6 and increased level of olanzapine	Mild elevation in AST levels	NA[1] NA[2]

† drug–drug interaction
[1] risk by Drugs.com interaction checker [14]
[2] risk by Liverpool COVID–19 Interactions checker [13]
NA – not available

regained only after complete reversal of rocuronium with a standard 200 mg bolus of sugammadex. Drug interaction between ritonavir and rocuronium was considered the most probable after excluding the impact of electrolyte disturbances and other pharmacodynamic interactions. More details about possible mechanisms of interactions are presented in table 4.

A case of a 64-year-old man with hypertension and hypercholesterolemia and COVID-19 was described by Leegwate et al. [35]. The patient was already treated with enalapril, amlodipine, and simvastatin for underlying medical conditions. Following the diagnosis of coronavirus disease, additional therapy started with hydroxychloroquine (600 mg loading dose and then 300 mg a day). On 3th day, a patient was transferred to ICU for mechanical ventilation. After 13 days, physicians prescribed remdesivir as an extended access program in the absence of improvement. Due to atrial fibrillation, 700 mg of amiodarone was administered two days later. On the 21st day, liver parameters suggested drug-induced liver injury caused by remdesivir. The authors rejected the possibility of such damage being caused by amiodarone as the cumulative dose was low, and acute amiodarone toxicity has an early onset, usually manifesting within 24 hours of administration. After discontinuation of extended treatment, parameters returned to normal in the next few days, and on the 48th day, a patient left ICU. The authors noticed significantly high levels of AST, ALT, alkaline phosphatase, bilirubin, and ɣ-glutamyltransferase two days after amiodarone administration. A probable interaction mechanism assumes inhibition of P-gp located on the hepatocyte membrane by amiodarone or hydroxychloroquine and increased remdesivir intrahepatocellular concentration manifested by liver injury.

Our systematic review included Sönmez Güngör et al. [36] describing ADRs observed in acute psychiatric patients with COVID-19 admitted to the special ward of Erenköy Mental Health and Neurological Diseases Hospital between 15 April and 15 June 2021. In that period, 4/23 (17.4%) of patients have experienced other than extrapyramidal ADRs, which are described below. The Naranjo scale assessed ADR to evaluate the probability due to the drug treatment. For example, one patient receiving risperidone 6 mg/day p.o. had mild constipation (Naranjo Score = 4), another treated with haloperidol 7.5 mg/day reported bradyarrhythmia (Naranjo Score = 6), and two patients manifested liver enzymes increase (Naranjo Score = 4 and 5). Additionally, researchers did not find a statistically significant relationship between potential variables and clinical outcomes.

In an observational single-center cohort study by Cantudo-Cuenca et al. [37], 152 of 174 patients experienced 417 real risk DDIs between COVID-19 therapy and 60 different concomitant medications.

A considerable number of interactions concerned hydroxychloroquine (52.9%) and lopinavir/ritonavir (43.2%). Real DDIs, according to ATC classification, are shown in figure 2. Despite analysis of real DDIs, there is no information in the publication about interactions between specific drug combinations.

In a retrospective cohort study by Martinez-Lopez-de-Castro et al. (16), the authors mainly focused on DDIs leading to QT-prolongation; however other clinical consequences were also noticed. PIs were involved in 16 out of 19 drug combinations, which are presented in table 5, whereas one of them concerned tacrolimus and hydroxychloroquine and is described in the immunosuppressant DDIs section of this systematic review. The second was related to the co-administration of azithromycin and hydroxychloroquine resulting in skin reaction and was noticed in 7 out of 80 patients. Finally, in the last report, the authors described an interaction between metamizole and interferon beta-1b, leading to hematological toxicity.

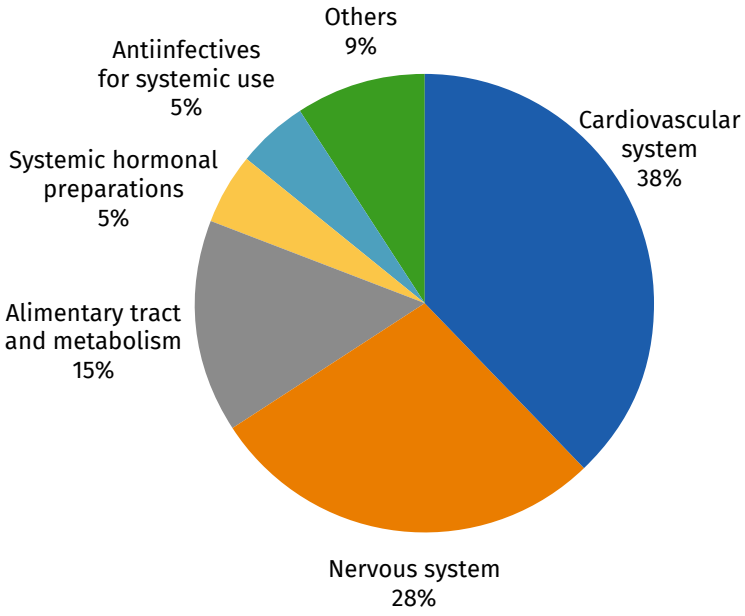

Figure 2. Real DDIs with COVID-19 treatment according to ATC classification.

Discussion

The Coronavirus 2019 (COVID-19) pandemic has caused a worldwide public health crisis lacking proven effective therapies. As a result, the medical community has turned to experimental therapies in the sickest hospitalized patients and ambulatory settings as pre-emptive management. Unfortunately, some drugs used as an anti-COVID-19 treatment have the propensity to DDIs that are potentially harmful [38, 39]. In our systematic review, chloroquine or hydroxychloroquine and lopinavir/ritonavir treatment concerned the highest risk of interactions.

Most papers in the review concerned DDIs between immunosuppressants and medication used to treat the coronavirus disease. Among them, the most significant risk of interactions was observed using lopinavir/ritonavir due to CYP3A4 and intestinal P-gp inhibition as well as slightly also CYP2D6. Based on such a mechanism, ritonavir causes blood level fluctuations in most immunosuppressants, which are metabolized by CYP450 and eliminated via P-gp [40, 41]. In the Van Maarseveen et al. study, tacrolimus clearance was about 40-fold lower (472.0 vs. 11.7 mL/min), and elimination half-life 10-fold higher (12.9 vs.117.0 hours) in HIV patients treated by ritonavir than HIV-negative KT patients [42]. Due to extended elimination, Prajakta et al. created a pharmacokinetic model to adjust tacrolimus dosage to the co-administration of the ritonavir antiviral therapy. To achieve adequate immunosuppression and low risk of toxic effects, tacrolimus dosage required reduction to 0.5 mg every 7 or 14 days [43]. In the case of mTOR inhibitors like sirolimus or everolimus, transplant guidelines recommended discontinuation and changing treatment for calcineurin inhibitors [22, 44]. It is driven mainly by pulmonary adverse effects like drug-induced pneumonitis or interstitial lung disease [40]. CYP3A4 also metabolizes sirolimus and everolimus, so in co-administration with PIs, sirolimus treatment requires 50–90% dosage reduction. In the case of everolimus, Meziyerh et al. highlighted the need to discontinue such therapy [22, 44]. Martinez-Lopez-de-Castro et al. found an interaction between tacrolimus and HCQ, leading to increased tacrolimus blood levels [26]. According to their findings, the most probable mechanism of interaction increasing tacrolimus level was inhibition of P-gp by HCQ, leading to decreased tacrolimus elimination [45].

The second-largest group of articles included in the review described the interaction of COVID-19 treatment caused QT-prolongation. Chloroquine, hydroxychloroquine, azithromycin, and lopinavir/ritonavir may increase QT interval in monotherapy [7]. Based on the above, most drug regimens for COVID-19 therapy are at risk of combining at least two or more agents with the possibility of QT-prolongation properties. The highest chance of QT-prolongation in monotherapy is associated with the use of HCQ [46]. Due to off-label treatment protocols, patients treated by HCQ with concurrent azithromycin have a statistically higher chance of QT-prolongation [47, 48].

Table 5. Interactions with clinically significant consequences other than QTC interval prolongation for lopinavir/ritonavir treatment.

Concomitant drugs	n (patients with clinical consequences/ patients with interaction)	Type of clinical consequence	Risk by checkers
Hydroxychloroquine	1/147	Hyperglycaemia	Major[1] NA[2]
Methylprednisolone or prednisone	10/36		Major for methylprednisolone and moderate for prednisone[1] No interaction[2]
Hydroxychloroquine	3/147	Gastrointestinal disorders	Major[1] NA[2]
Azithromycin	5/43		Moderate[1] Potential interaction[2]
Hydroxychloroquine	1/147	Skin reaction	Major[1] NA[2]
Lithium	1/4	Alteration of the concentration of blood levels	Moderate[1] NA[2]
Aripiprazole	1/1		Moderate[1] NA[2]
Fentanyl	1/10		Major[1] NA[2]
Digoxin	1/3		Moderate[1] NA[2]
Midazolam or diazepam	3/13	Increased sedative effect	Major for midazolam and moderate for diazepam[1] NA[2]
Hydroxychloroquine	1/147	Psychiatric disorder	Major[1] NA[2]
Alprazolam	1/13		Major[1] NA[2]
Amlodipine	2/8	Increased oedema	Moderate[1] NA[2]
Simvastatin	2/2	Liver toxicity	Major[1] NA[2]
Valproate	1/1	Seizures	Moderate[1] NA[2]
Propofol	1/6	Increased triglyceride level	Moderate[1] NA[2]

[1] risk by Drugs.com interaction checker [14]
[2] risk by Liverpool COVID-19 Interactions checker [13]
NA – not available

Additionally, in the Kim et al. study, patients in an HCQ and azithromycin and a higher dose of HCQ groups have a statistically higher chance of QT prolongation (defined by QTc interval > 500 ms or increase QTc at least 60ms) than patients in a control group [49]. It is related to the additive cardiotoxic effect of both drugs, and CYP3A4 inhibition by azithromycin caused increasing levels of HCQ [7]. In the case of lopinavir/ritonavir, there is no reliable data about causing QT prolongation, but CYP3A4 inhibitors can increase blood levels of other risky drugs like HCQ [7, 50]. Moreover, according to SmPC information about cardiac events reported in lopinavir/ritonavir pre-clinical studies, the co-administration with other drugs with the same risk should be carefully re-considered.

One of the recommended supporting therapy for COVID-19 is anticoagulation. However, anticoagulants are among the highest-risk drug classes to cause adverse events and have a narrow therapeutic index [38, 51]. Furthermore, all DOACs, as a substrate for P-gp, are susceptible to changes in efflux processes caused by P-gp inhibitors or inductors. Similarly, apixaban, rivaroxaban, and 4% of edoxaban are metabolized in the liver primarily by CYP3A4 [52]. According to this, the main DAOC and COVID-19 treatment co-administration is a potential risk of inhibition of CYP450 and P-gp. In Testa et al. study, 20 of 32 patients with previously administered DOACs and treated for COVID-19 by PIs were required to stop anticoagulant therapy due to a mean of 6.14 times higher blood levels than before hospitalization [33].

Of particular interest were relatively rare DDI interactions encountered in critical care settings. In one of the case reports, the unpredictability of pharmacokinetics of muscle relaxants leads to difficult weaning of mechanical ventilation. Only timely recognition of the prolonged muscle block by rocuronium allowed for a successful therapeutic approach and complete reversal using sugammadex, which in turn allowed to support spontaneous ventilation [34] successfully. The other study [35] described detrimental DDI leading to temporary liver dysfunction, most likely caused by retroviral agent administration. Although, in this case, multiple other explanatory mechanisms were evaluated, such as direct amiodarone toxicity or the impact of critical illness, the above interaction was deemed the most likely. The drugs.com checker also suggests potential interactions between lopinavir/ritonavir and commonly used sedative agents such as midazolam and diazepam, leading to unanticipated prolongation of medicines action. The other interaction suggested by such a database is related to the increase of triglyceride levels during propofol infusion. Although such an increase in separation is not particularly detrimental, in combination with other signs and symptoms may be pathognomonic of propofol infusion syndrome, hence warranting further studies.

Conclusions

In conclusion, our systematic review identified a plethora of different DDI relevant to all branches of medicine. The tertiary services such as transplant medicine need to be aware of interactions between retroviral medications and antirejection regimes, leading to unpredictable high levels of the latter. The critical care physicians need to bear in mind the potential impact of the slow elimination of sedatives and muscle relaxants, impeding patient recovery. Drug interaction leading to prolongation of QT interval may cause life-threatening arrhythmias, requiring special vigilance to monitor for such occurrences. Increased DOAC levels could indicate a higher risk of bleeding in anticoagulated patients. Therefore we would urge all physicians, pharmacologists, and clinical pharmacists involved in the treatment of COVID-19 disease to familiarise themselves with such interactions to minimize the risk for the patients under their care.

References

1. World Health Organisation. WHO Coronavirus (COVID-19) Dashboard. (online) 2022. Available online: https://covid19.who.int/. Access 6.04.2022.
2. Sharif N, Alzahrani KJ, Ahmed SN, Dey SK. Efficacy, Immunogenicity and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis. *Front Immunol.* 2021; 12. doi: 10.3389/fimmu.2021.714170.
3. Our World in Data. Coronavirus (COVID-19) Vaccinations. (online) 2022. Available online: https://ourworldindata.org/covid-vaccinations. Access 6.04.2022.
4. Tsang HF, Chan LWC, Cho WCS, Yu ACS, Yim AKY, Chan AKC, et al. An update on COVID-19 pandemic: the epidemiology, pathogenesis, prevention and treatment strategies. *Expert Rev Anti Infect Ther.* 2021; 19: 877–888. doi: 10.1080/14787210.2021.1863146.
5. Bartoletti M, Azap O, Barac A, Bussini L, Ergonul O, Krause R, et al. ESCMID COVID-19 living guidelines: drug treatment and clinical management. *Clin Microbiol Infect.* 2022; 28: 222–238. doi: 10.1016/j.cmi.2021.11.007.
6. Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M, et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). *Int J Antimicrob Agents.* 2020; 56(2). doi: 10.1016/j.ijantimicag.2020.106080.
7. Zequn Z, Yujia W, Dingding Q, Jiangfang L. Off-label use of chloroquine, hydroxychloroquine, azithromycin and lopinavir/ritonavir in COVID-19 risks prolonging the QT interval by targeting the hERG channel. *Eur J Pharmacol.* 2021; 893. doi: 10.1016/j.ejphar.2020.173813.
8. Agarwal S, Agarwal SK. Lopinavir-Ritonavir in SARS--CoV-2 Infection and Drug-Drug Interactions with Cardioactive Medications. *Cardiovasc Drugs Ther.* 2021; 35: 427–440. doi: 10.1007/s10557-020-07070-1.
9. Rahman S, Singh K, Dhingra S, Charan J, Sharma P, Islam S, et al. The double burden of the COVID-19 pandemic and polypharmacy on geriatric population – public health implications. *Ther Clin Risk Manag.* 2020; 16: 1007–1022. doi: 10.2147/TCRM.S272908.
10. Iloanusi S, Mgbere O, Essien EJ. Polypharmacy among COVID-19 patients: A systematic review. *J Am Pharm Assoc.* 2021; 61: 14–25. doi: 10.1016/j.japh.2021.05.006.
11. Page MJ, McKenzie JE, Bossuyt P, Boutron I, Hoffmann TC, Mulrow CD, et al. The prisma 2020 statement: An updated guideline for reporting systematic reviews. *Med Flum.* 2021; 57: 444–465. doi: 10.21860/medflum2021_264903.
12. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan--a web and mobile app for systematic reviews. *Syst Rev.* 2016; 5. doi: 10.1186/s13643-016-0384-4.
13. The Liverpool Drug Interaction Group. Liverpool COVID-19 Interactions 2020. (online) 2022. Available online: https://www.covid19-druginteractions.org/checker%0Ahttps://www.covid19-druginteractions.org/interactions/2556. Access 1.02.2022.
14. Drugs.com Drug Interactions Checker. (online) 2022. Available online: https://www.drugs.com/drug_interactions.html. Access 1.02.2022.
15. Bauer AC, Franco RF, Manfro RC. Immunosuppression in Kidney Transplantation: State of the Art and Current Protocols. *Curr Pharm Des.* 2020; 26: 3440–3450. doi: 10.2174/1381612826666200521142448.
16. Kuypers DRJ. Immunotherapy in elderly transplant recipients: A guide to clinically significant drug interactions. *Drugs and Aging.* 2009; 26: 715–737. doi: 10.2165/11316480-000000000-00000.
17. Lam S, Partovi N, Ting LSL, Ensom MHH. Corticosteroid interactions with cyclosporine, tacrolimus, mycophenolate, and sirolimus: fact or fiction? *Ann Pharmacother.* 2008; 42: 1037–1047. doi: 10.1345/aph.1K628.
18. Bartiromo M, Borchi B, Botta A, Bagalà A, Lugli G, Tilli M, et al. Threatening drug-drug interaction in a kidney transplant patient with coronavirus disease 2019 (COVID-19). *Transpl Infect Dis.* 2020; 22. doi:10.1111/tid.13286.
19. Kim Y, Kwon O, Paek JH, Park WY, Jin K, Hyun M, et al. Two distinct cases with COVID-19 in kidney transplant recipients. *Am J Transplant.* 2020; 20: 2269–2275. doi: 10.1111/ajt.15947.
20. Vongchaiudomchoke T, Sawangduan V, Sinpanee T, Chalermphunchai N, Lelamali K, Noppakun K. Modification of immunosuppressive agents in a kidney transplant recipient with COVID-19 and acute kidney injury. *J Infect Dev Ctries.* 2021; 15: 1273–1276. doi: 10.3855/jidc.13176.
21. Thammathiwat T, Tungsanga S, Tiankanon K, Torvorapanit P, Chumpangern W, Udomkarnjananun S, et al. A case of successful treatment of severe COVID-19 pneumonia with favipiravir and tocilizumab in post-kidney transplant recipient. *Transpl Infect Dis.* 2021; 23. doi: 10.1111/tid.13388.
22. Meziyerh S, Zwart TC, van Etten RW, Janson JA, van Gelder T, Alwayn IPJ, et al. Severe COVID-19 in a renal transplant recipient: A focus on pharmacokinetics. *Am J Transplant.* 2020; 20: 1896–1901. doi: 10.1111/ajt.15943.

23. Ra R, Kim JS, Jeong KH, Hwang HS. COVID-19 and sirolimus treatment in a kidney transplant recipient. *Exp Clin Transplant*. 2021; 19: 977–980. doi: 10.6002/ect.2021.0232.
24. Saez-Giménez B, Berastegui C, Barrecheguren M, Revilla-López E, Los Arcos I, Alonso R, et al. COVID-19 in lung transplant recipients: A multicenter study. *Am J Transplant*. 2021; 21: 1816–1824. doi: 10.1111/ajt.16364.
25. Miarons M, Larrosa-García M, García-García S, Los-Arcos I, Moreso F, Berastegui C, et al. COVID-19 in Solid Organ Transplantation: A Matched Retrospective Cohort Study and Evaluation of Immunosuppression Management. *Transplantation*. 2021; 105: 138–150. doi: 10.1097/TP.0000000000003460.
26. Martínez-López-de-Castro N, Samartín-Ucha M, Paradela-Carreiro A, Pérez-Landeiro A, Inaraja-Bobo MT, Álvarez-Payero M, et al. Real-world prevalence and consequences of potential drug--drug interactions in the first-wave COVID-19 treatments. *J Clin Pharm Ther*. 2021; 46: 724–730. doi: 10.1111/jcpt.13337.
27. Hooks M, Bart B, Vardeny O, Westanmo A, Adabag S. Effects of hydroxychloroquine treatment on QT interval. *Hear Rhythm*. 2020; 17: 1930–1935. doi: 10.1016/j.hrthm.2020.06.029.
28. Charbit B, Rosier A, Bollens D, Boccara F, Boelle PY, Koubaa A, et al. Relationship between HIV protease inhibitors and QTc interval duration in HIV-infected patients: A cross-sectional study. *Br J Clin Pharmacol*. 2009; 67: 76–82. doi: 10.1111/j.1365--2125.2008.03332.x.
29. Zhu S, Wang J, Wang Y, Chu J, Liu Y, Chen X, et al. QTc prolongation during antiviral therapy in two COVID-19 patients. *J Clin Pharm Ther*. 2020; 45: 1190–1193. doi:10.1111/jcpt.13183.
30. Anmella G, Arbelo N, Fico G, Murru A, Llach CD, Madero S, et al. COVID-19 inpatients with psychiatric disorders: Real-world clinical recommendations from an expert team in consultation-liaison psychiatry. *J Affect Disord*. 2020; 274: 1062–1067. doi: 10.1016/j.jad.2020.05.149.
31. Koh HM, Chong PF, Tan JN, Chidambaram SK, Chua HJ. QT prolongation associated with hydroxychloroquine and protease inhibitors in COVID-19. *J Clin Pharm Ther*. 2021; 46: 800–806. doi: 10.1111/jcpt.13356.
32. Launay M, Demartin AL, Ragey SP, Mismetti P, Botelho-Nevers E, Delavenne X. Severe Inflammation, Acute Kidney Injury, and Drug-Drug Interaction: Triple Penalty for Prolonged Elimination of Apixaban in Patients With Coronavirus Disease 2019: A Grand Round. *Ther Drug Monit*. 2021; 43: 455–458. doi: 10.1097/FTD.0000000000000899.
33. Testa S, Prandoni P, Paoletti O, Morandini R, Tala M, Dellanoce C, et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. *J Thromb Haemost*. 2020; 18: 1320–1323. doi: 10.1111/jth.14871.
34. Domingo-Chiva E, Monsalve-Naharro J, Gerónimo-Pardo M. Myopathy, residual effect of rocuronium, or both? A possible ritonavir-rocuronium interaction interfering weaning from mechanical ventilation in a patient with COVID-19 pneumonia. *J Anaesthesiol Clin Pharmacol*. 2020; 36: 556–558. doi: 10.4103/joacp.JOACP_346_20.
35. Leegwater E, Strik A, Wilms EB, Bosma LBE, Burger DM, Ottens TH, et al. Drug-induced Liver Injury in a Patient with Coronavirus Disease 2019: Potential Interaction of Remdesivir with P-Glycoprotein Inhibitors. *Clin Infect Dis*. 2021; 72: 1256–1258. doi: 10.1093/cid/ciaa883.
36. Sönmez Güngör E, Yalçın M, Yerebakan Tüzer M, Beşikçi Keleş D, Öcek Baş T, Ergelen M, et al. Adverse drug reactions associated with concurrent acute psychiatric treatment and COVID-19 drug therapy. *Int J Psychiatry Clin Pract*. 2021; 25: 142–146. doi: 10.1080/13651501.2020.1843182.
37. Cantudo-Cuenca MD, Gutiérrez-Pizarraya A, Pinilla-Fernández A, Contreras-Macías E, Fernández-Fuertes M, Lao-Domínguez FA, et al. Drug-drug interactions between treatment specific pharmacotherapy and concomitant medication in patients with COVID-19 in the first wave in Spain. *Sci Rep*. 2021; 11. doi: 10.1038/s41598-021-91953-2.
38. Hodge C, Marra F, Marzolini C, Boyle A, Gibbons S, Siccardi M, et al. Drug interactions: A review of the unseen danger of experimental COVID-19 therapies. *J Antimicrob Chemother*. 2020; 75: 3417–3424. doi: 10.1093/jac/dkaa340.
39. Lin M, Dong HY, Xie HZ, Li YM, Jia L. Why do we lack a specific magic anti-COVID-19 drug? Analyses and solutions. *Drug Discov Today*. 2021; 26: 631–636. doi: 10.1016/j.drudis.2020.12.010.
40. Mirjalili M, Shafiekhani M, Vazin A. Coronavirus disease 2019 (COVID-19) and transplantation: Pharmacotherapeutic management of immunosuppression regimen. *Ther Clin Risk Manag*. 2020; 16: 617–629. doi: 10.2147/TCRM.S256246.
41. Bickel M, Anadol E, Vogel M, Hofmann WP, von Hentig N, Kuetscher J, et al. Daily dosing of tacrolimus in patients treated with HIV-1 therapy containing a ritonavir-boosted protease inhibitor or raltegravir. *J Antimicrob Chemother*. 2010; 65: 999–1004. doi: 10.1093/jac/dkq054.
42. Van Maarseveen EM, Crommelin HA, Mudrikova T, Van Den Broek MPH, Van Zuilen AD. Pretransplantation pharmacokinetic curves of tacrolimus in HIV-infected patients on ritonavir-containing cART: A pilot study. *Transplantation*. 2013; 95: 397–402. doi: 10.1097/TP.0b013e3182734651.
43. Badri PS, Parikh A, Coakley EP, Ding B, Awni WM, Dutta S, et al. Pharmacokinetics of Tacrolimus and Cyclosporine in Liver Transplant Recipients Receiving 3 Direct-Acting Antivirals as Treatment for Hepatitis C Infection. *Ther Drug Monit*. 2016; 38: 640–645. doi: 10.1097/FTD.0000000000000315.
44. Barau C, Blouin P, Creput C, Taburet AM, Durrbach A, Furlan V. Effect of coadministered HIV-protease inhibitors on tacrolimus and sirolimus blood concentrations in a kidney transplant recipients. *Fundam Clin Pharmacol*. 2009; 23: 423–425. doi: 10.1111/j.1472-8206.2009.00706.x.
45. Weiss J, Bajraktari-Sylejmani G, Haefeli WE. Interaction of hydroxychloroquine with pharmacokinetically important drug transporters. *Pharmaceutics*. 2020; 12: 1–13. doi: 10.3390/pharmaceutics12100919.
46. Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. *Clin Toxicol*. 2006; 44: 173–175. doi: 10.1080/15563650500514558.
47. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT Interval Prolongation Associated with Use of Hydroxychloroquine with or without Concomitant Azithromycin among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020; 5: 1036–1041. doi: 10.1001/jamacardio.2020.1834.
48. Bessière F, Roccia H, Delinière A, Charrière R, Chevalier P, Argaud L, et al. Assessment of QT Intervals in a Case Series of Patients with Coronavirus Disease 2019 (COVID-19) Infection Treated with Hydroxychloroquine Alone or in Combination with Azithromycin in an Intensive Care Unit. *JAMA Cardiol*. 2020; 5: 1067–1069. doi: 10.1001/jamacardio.2020.1787.
49. Kim MS, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. *PLoS Med*. 2020; 17. doi: 10.1371/journal.pmed.1003501.
50. Soliman EZ, Lundgren JD, Roediger MP, Duprez DA, Temesgen Z, Bickel M, et al. Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. *Aids*. 2011; 25: 367–377. doi: 10.1097/QAD.0b013e328341dcc0.
51. Vazquez SR. Drug-drug interactions in an era of multiple anticoagulants: A focus on clinically relevant drug interactions. *Hematol*. 2018; 2018: 339–347. doi: 10.1182/asheducation-2018.1.339.
52. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-Vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015; 17: 1467–1507. doi: 10.1093/europace/euv309.