




Drug–Drug Interactions and Prescription Appropriateness in Patients with COVID-19: A Retrospective Analysis from a Reference Hospital in Northern Italy

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Abstract

Background Patients hospitalised with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2; coronavirus 2019 disease (COVID-19)] infection are frequently older with co-morbidities and receiving polypharmacy, all of which are known risk factors for drug–drug interactions (DDIs). The pharmacological burden may be further aggravated by the addition of treatments for COVID-19.

Objective The aim of this study was to assess the risk of potential DDIs upon admission and during hospitalisation in patients with COVID-19 treated at our hospital.

Methods We retrospectively analysed 502 patients with COVID-19 (mean age 61 ± 16 years, range 15–99) treated at our hospital with a proven diagnosis of SARS-CoV-2 infection hospitalised between 21 February and 30 April 2020 and treated with at least two drugs.

Results Overall, 68% of our patients with COVID-19 were exposed to at least one potential DDI, and 55% were exposed to at least one potentially severe DDI. The proportion of patients experiencing potentially severe DDIs increased from 22% upon admission to 80% during hospitalisation. Furosemide, amiodarone and quetiapine were the main drivers of potentially severe DDIs upon admission, and hydroxychloroquine and particularly lopinavir/ritonavir were the main drivers during hospitalisation. The majority of potentially severe DDIs carried an increased risk of cardiotoxicity. No potentially severe DDIs were identified in relation to tocilizumab and remdesivir.

Conclusions Among hospitalised patients with COVID-19, concomitant treatment with lopinavir/ritonavir and hydroxychloroquine led to a dramatic increase in the number of potentially severe DDIs. Given the high risk of cardiotoxicity and the scant and conflicting data concerning their efficacy in treating SARS-CoV-2 infection, the use of lopinavir/ritonavir and hydroxychloroquine in patients with COVID-19 with polypharmacy needs to be carefully considered.

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1 Background

As of 24 August 2020, the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection had affected more than 23 million people worldwide and led to nearly 800,000 deaths (update available at <https://coronavirus.jhu.edu/map.html>). A number of important risk factors associated with a negative prognosis in patients with coronavirus 2019 disease (COVID-19) have been identified, including aging, male sex, ethnicity, and the presence of co-morbidities such as hypertension, diabetes mellitus, obesity and cardiovascular, lung and/or kidney diseases [1–3].

Regardless of SARS-CoV-2 infection, aging and co-morbidities are well recognised independent drivers of the development of drug–drug interactions (DDIs) [4–6]. Aging

Key Points

Of patients hospitalised with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2; coronavirus 2019 disease (COVID-19)], 50% are elderly (> 65 years), with co-morbidities and receiving polypharmacy, all of which are known risk factors for drug–drug interactions (DDIs). The pharmacological burden may be further aggravated by the addition of treatments for SARS-CoV-2 infection.

We demonstrated that, in hospitalised patients with COVID-19, concomitant treatment with lopinavir/ritonavir and hydroxychloroquine led to a dramatic increase in the number of potentially severe DDIs.

Given the high risk of cardiotoxicity and the scant and conflicting data concerning their efficacy in treating SARS-CoV-2 infection, the use of lopinavir/ritonavir and hydroxychloroquine in patients with COVID-19 with polypharmacy needs to be carefully considered.

is associated with physiological changes that significantly affect the pharmacokinetics and pharmacodynamics of various drugs, thus increasing the risk of inappropriate dosing and the development of drug-related toxicity [7, 8]. The optimal control of age-related and age-unrelated co-morbidities usually requires polypharmacy, thus further increasing the risk of DDIs [9–11]. This situation may be aggravated in patients with COVID-19 as the polypharmacy burden is increased by the addition of specific treatments for SARS-CoV-2 infection. The HIV protease inhibitors lopinavir and darunavir (the first drugs tested as SARS-CoV-2 inhibitors) are co-administered with the pharmaco-enhancers ritonavir or cobicistat, both of which are known to be responsible for pharmacokinetic-related DDIs because of their modulatory effects on cytochrome and non-cytochrome enzymes and drug transporters [12]. Chloroquine, hydroxychloroquine and azithromycin have also been proposed for the treatment of COVID-19, but they may intensify pharmacodynamic-related DDIs because the negative effects on the heart may exacerbate the cardiac toxicity of chronically administered drugs aimed at treating co-morbidities [13–15]. Additionally, patients hospitalized for COVID-19 may receive other drugs for the treatment of specific symptoms, further aggravating their overall pharmacological burden. Taken together, this puts patients with COVID-19 at extremely high risk of inappropriate medication prescriptions, potentially severe DDIs, and potentially worse clinical outcomes, independent of the severity of SARS-CoV-2 infection.

Balanced and safe prescribing is difficult to achieve in older adults with multiple co-morbid diseases. For this

reason, great efforts have been made in the search for interventions to improve the efficacy, safety and appropriateness of prescriptions in this vulnerable population. Among these interventions, the avoidance of medications that are considered inappropriate, i.e. potentially inappropriate medications (PIMs), has been considered a valuable treatment option. Similarly, paramount to medication safety in this population is prudent attention to drug selection and drug dosing and monitoring for effectiveness as well as drug and disease interactions. To address these issues, implicit and explicit medication use criteria have been developed to help guide medication use in older adults and enable measurement of the quality of prescribing. The various computerised prescription support systems developed recently allow the scoring of DDIs and the identification of PIMs on the basis of specific rules, such as the updated Beers criteria and the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) [16–19]. Another key marker of appropriate medication prescription is the anti-cholinergic burden (ACB), which refers to the cumulative effect of taking one or more medications with anticholinergic activity [20]. Indeed, it has been clearly shown that the cumulative effect of multiple medicines with anti-cholinergic properties can have an adverse impact on cognition and physical function and increase the risk of falls and mortality [20]. However, Beers criteria, STOPP and the ACB have only been assessed in patients aged > 65 years [16–20].

The aim of this study was to assess the risk and severity of potential DDIs in patients with COVID-19 admitted to our hospital and then evaluate PIMs and the ACB in the subset of patients aged > 65 years. All of the assessments were made upon admission and during hospitalisation in order to be able to establish the potential contribution of SARS-CoV-2 treatments to the total pharmacological burden in terms of DDIs, PIMs and the ACB.

2 Methods

2.1 Patient Selection

We searched the database of the Department of Infectious Diseases of Luigi Sacco Hospital (Milan, Italy) for all patients with a proven diagnosis of SARS-CoV-2 infection (a throat swab positive for viral nucleic acid) hospitalised between 21 February and 30 April 2020 and treated with at least two drugs. All drugs were considered regardless of COVID-19 treatments. The medical records were also reviewed to record the main demographic and co-morbidity data. All co-morbidities extracted from the electronic records were included in the statistical analyses. Information concerning pharmacological treatments was collected upon admission and during hospitalisation. Given the

heterogeneity of the drugs administered, concomitant medications were classified according to the anatomical therapeutic chemical classification system, which is a drug classification system that categorizes the active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

This retrospective study was conducted using data collected for clinical purposes, all of which had been previously made anonymous in accordance with the requirements of the Italian Personal Data Protection Code (Legislative Decree No. 196/2003) and the general authorisations issued by the Italian Data Protection Authority. The study was approved by our hospital's ethics committee (Comitato Etico Interaziendale Area 1). All of the patients included in the study signed an informed consent form for the administration of off-label treatments.

2.2 Computerised Prescription Support System

The appropriateness of drug prescriptions was assessed using INTERcheck[®], a Computerized Prescription Support System (CPSS) developed by the Istituto di Ricerche Farmacologiche Mario Negri IRCCS, which stores information on explicit criteria for PIMs, anticholinergic load, potential DDIs, dose adjustment in cases of renal impairment and modality for drug withdrawals (dose tapering) [21–26]. It classifies the potential DDIs according to their clinical relevance: contraindicated (D, drug combinations that should be avoided); major (C, drug combinations requiring close monitoring for potentially serious clinical consequences, such as severe adverse effects or lack of clinical efficacy); moderate (B, drug combinations requiring dose adjustment and/or drug concentration monitoring); minor (A, drug combinations with no known clinical relevance). The database of DDIs is updated weekly. INTERCheck has already been validated in clinical practice and been found to reduce the number of patients receiving PIMs and those exposed to potentially severe DDIs in a geriatric ward and in a sample of nursing homes. INTERCheck is commonly used in nursing homes and hospital settings to evaluate the appropriateness of drug prescription and optimize medications in multimorbid older patients acutely admitted to hospital medical wards. INTERCheck will be used as a reference CPSS in Italy to improve the appropriateness of prescribing. The tool is freely available on request.

Class C and D DDIs were pooled and considered potentially severe DDIs in the subgroup analyses. PIMs were defined using Beers criteria. The ACB was investigated using two threshold values: ≥ 3 and ≥ 5 , indicating a risk and a high risk, respectively, of adverse events [20]. DDIs were assessed in all patients with COVID-19, whereas PIMs (through the application of the Beers criteria) and the ACB were assessed only in those aged > 65 years.

The risk of drugs inducing QT prolongation or Torsade de Pointes (TdP) was scored according to the Credible Meds Website (<https://www.crediblemeds.org>), which categorizes drugs as having a 'known', 'possible' or 'conditional' risk of QT prolongation or TdP.

2.3 Statistical Analyses

The frequency distribution data are expressed as absolute numbers and percentages and all other measures as mean \pm standard deviation. The data refer to the population as a whole and were stratified on the basis of sex or time of assessment (upon admission or during hospitalisation). Differences in the risk of DDIs, PIMs and ACB score upon admission and during hospitalization were tested using Student's *t* test for continuous variables and Pearson's chi-squared test for dichotomous and unordered categorical data.

3 Results

3.1 Patient Characteristics

During the observation period, 502 patients with proven SARS-CoV-2 infection were hospitalised in the Department of Infectious Diseases of Luigi Sacco Hospital (Milan, Italy). Male sex predominated (67%), and the mean age was 61 ± 16 years (range 15–99). As Table 1 shows, 89% had at least one co-morbidity, primarily cardiovascular (28%) and metabolic diseases (18%), with no significant difference between males and females. In total, 399 patients (79%) were concomitantly treated with at least two drugs: 56% upon admission and 73% during hospitalisation.

Figure 1 demonstrates the distribution of the main drug classes. The most frequent at the time of admission were antihypertensive agents ($n=220$), oral antidiabetic drugs ($n=77$), proton pump inhibitors ($n=62$) and diuretics ($n=60$), and the frequency remained substantially unchanged during hospitalisation (199, 65, 55 and 61, respectively). During hospitalisation, there were significant increases in the use of corticosteroids (24 to 120, $p < 0.01$), immunosuppressants (3–89, $p < 0.01$; 91% tocilizumab), antibiotics (2 to 190, $p < 0.01$; 28% ceftriaxone, 18% piperacillin/tazobactam, 13% azithromycin and 9% meropenem), and heparins (1–91, $p < 0.01$). Among the drugs administered only during hospitalisation (not included in Fig. 1), 320 patients received hydroxychloroquine, 256 lopinavir/ritonavir and 70 remdesivir (sometimes in combination).

3.2 Drug–Drug Interactions

Of the 399 patients with COVID-19 treated with at least two drugs, 271 (68%) were exposed to at least one potential

Table 1 Characteristics of patients infected with SARS-CoV-2

Clinical features	Overall	Females	Males
Patients, <i>n</i>	502	164 (33)	338 (67)
Age, years	61 ± 16	60 ± 18	61 ± 16
Patients with at least one comorbidity	449	142 (32)	307 (68)
Number of co-morbidities ^a	755	261	494
Comorbidities per patient, <i>n</i>	1.7	1.8	1.6
Cardiovascular diseases	214 (28)	69 (26)	145 (29)
Metabolic diseases	135 (18)	56 (21)	79 (16)
Lung diseases	69 (8)	29 (7)	40 (8)
Oncological diseases	46 (6)	14 (5)	32 (6)
Kidney diseases	34 (5)	10 (4)	24 (5)
Immune diseases	28 (4)	9 (3)	19 (4)
Chronic infectious diseases	28 (4)	8 (3)	20 (4)
Psychiatric diseases	20 (3)	9 (3)	11 (2)
Others	181 (24)	57 (28)	124 (26)

Data are presented as mean ± standard deviation or *N* (%) unless otherwise indicated

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

^aSome patients had more than one comorbidity

DDI, 55% of which were classified as potentially severe (class C+D of the INTERcheck[®] DDI scoring system). As shown in Table 2, the number of patients with at least one DDI increased from 131 (46%) upon admission to 312

(85%) during hospitalisation, and the number with at least one potentially severe DDI increased from 62 (22%) to 294 (80%). Consistently, hospitalisation was associated with a twofold increase in class B + C DDIs, and an eightfold increase in class D DDIs (Fig. 2).

Tables 3 and 4 describe in detail the potential class D DDIs observed upon admission and during hospitalisation. The main drivers of the DDIs upon admission were the diuretic furosemide, the anti-arrhythmic amiodarone, the anti-psychotic quetiapine and two β-agonist bronchodilators; all these DDIs were associated with an increased risk of cardiotoxicity (QT prolongation). A reduced effect of clopidogrel or an increased risk of methotrexate toxicity due to concomitant proton pump inhibitor was recorded in five cases (Table 3).

Table 4 shows that the large majority of class D DDIs observed during hospitalisation increased the risk of QT prolongation (88%) and that these were mainly driven by lopinavir/ritonavir plus hydroxychloroquine (24%), lopinavir/ritonavir plus azithromycin (8%), hydroxychloroquine plus piperacillin (8%), lopinavir/ritonavir plus piperacillin (7%), and hydroxychloroquine plus azithromycin (6%). According to the Credible Meds website, azithromycin and hydroxychloroquine are classified as ‘known risk’, lopinavir/ritonavir as a ‘potential risk’ and piperacillin and quetiapine as ‘conditional risk’ for QT prolongation/TdP.

Lopinavir/ritonavir was also mainly responsible for the class D DDIs, increasing the risk of statin-induced myopathy

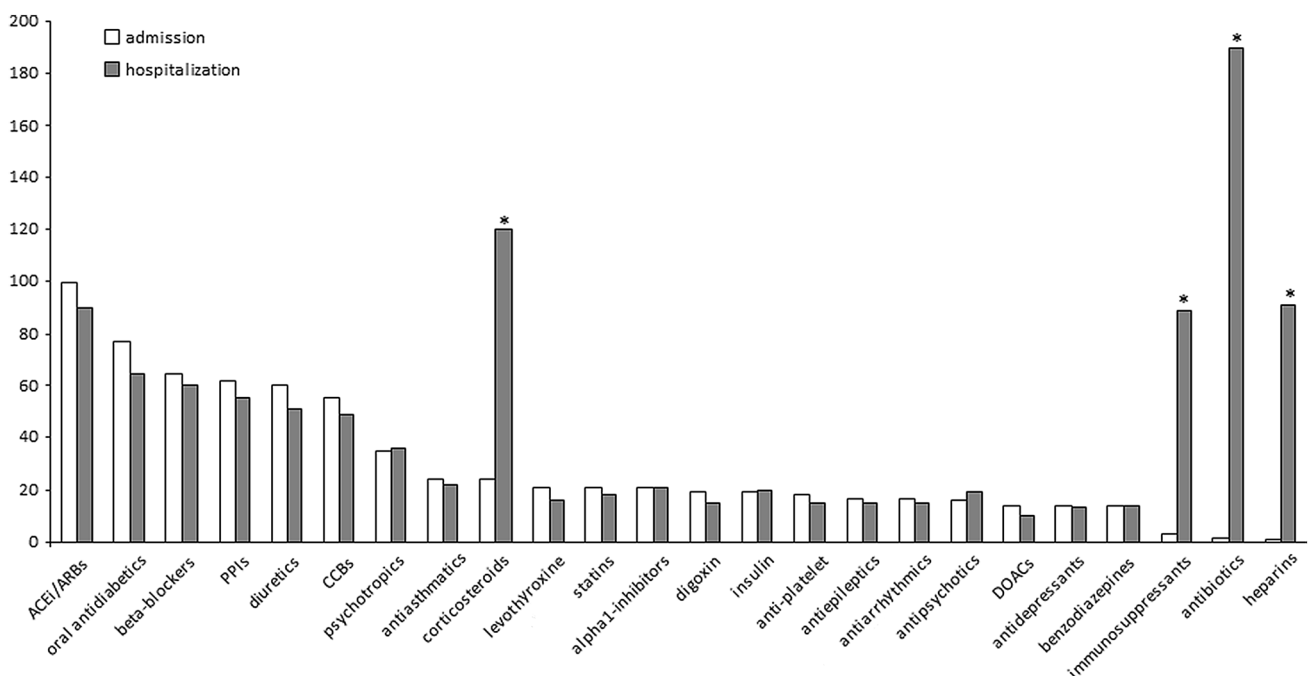


Fig. 1 Distribution of the main drug classes present upon admission and during hospitalisation (data are given as absolute numbers). ACEi angiotensin-converting enzyme inhibitors, ARBs angiotensin-receptor

blockers, CCBs calcium channel blockers, DOACs direct-acting oral anticoagulants, PPIs proton pump inhibitors. **p* < 0.01 vs. admission

Table 2 Pharmacological burden of patients infected with SARS-CoV-2 upon admission and during hospitalization (we considered all drugs regardless of COVID-19 treatments)

Clinical features	Overall	Upon admission	During hospitalisation
Patients treated with at least two drugs	399	285	367
Age, years	64 ± 14	66 ± 14	62 ± 15
Women	212 (33)	101 (35)	111 (30)
Number of drugs	5.6 ± 4.1	3.6 ± 2.6	7.3 ± 4.3
Total DDIs ^a	2160	478	2160*
Severe DDIs ^a	1329	134	1257*
Patients with at least one DDI	271 (68)	131 (46)	312 (85)*
Patients with at least one potentially severe DDI	219 (55)	62 (22)	294 (80)*
Patients aged > 65 years	201 (50)	155 (54)	155 (42)
Patients with at least one PIM ^a	172 (86)	147 (95)	137 (88)
ACB score	1.8 ± 1.2	1.8 ± 1.2	1.8 ± 1.2
Patients aged > 65 years with an ABC score of ≥ 3	39 (19)	19 (12)	21 (14)
Patients aged > 65 years with an ABC score of ≥ 5	5 (2.5)	2 (1.3)	3 (1.9)

Data are presented as n, mean ± standard deviation or N (%) unless otherwise indicated

ACB anti-cholinergic burden, DDI drug-drug interaction, PIM potentially inappropriate medication according to Beers criteria

^aSome patients experienced more than one DDI and/or PIM

* $p < 0.01$ vs. admission

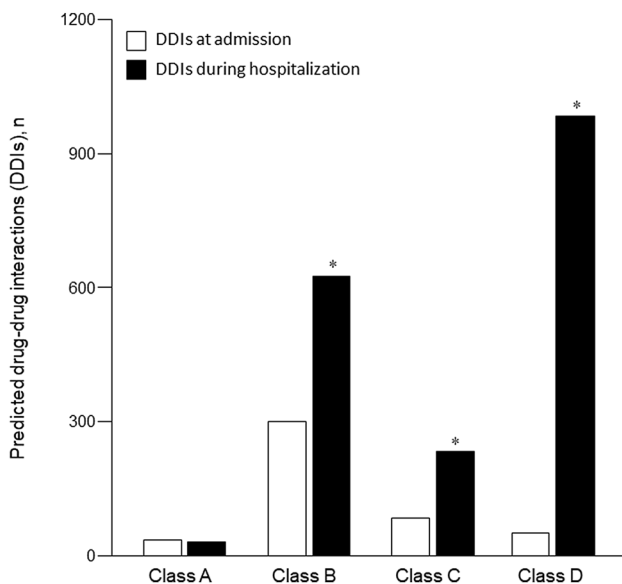


Fig. 2 Distribution of predicted DDIs upon admission and during hospitalisation. Class A: minor (clinically irrelevant interaction); class B: moderate (interaction associated with an uncertain or variable event); class C: major (interaction associated with a serious event that can be managed); and class D: contraindicated or very severe (interaction potentially associated with a serious event; co-administration should be avoided or careful monitoring established). * $p < 0.01$ vs. admission

(3.8%), benzodiazepine-induced central nervous system depression (2.2%), altered anti-thrombotic responses (2.0%) and corticosteroid-induced Cushing-like syndrome (1.6%). Tocilizumab and remdesivir were not associated with any class D DDI.

3.3 Potentially Inappropriate Medications and Anti-Cholinergic Burden in Patients with COVID-19 Aged > 65 Years

Of the 399 patients with COVID-19, 200 were aged > 65 years (50%). As shown in Table 2, the large majority (95%) had at least one PIM upon admission, based on the updated Beers criteria, a total of 267 Beers rule violations (data not shown); hospitalisation did not significantly reduce the PIMs (88% of patients had at least one PIM, a total of 264 Beers rule violations). ACB scores of ≥ 3 or ≥ 5 were recorded in 19% and 2.5% of the patients, respectively, with no significant difference between admission and hospitalisation (Table 2).

4 Discussion

The main finding of this study is that hospitalised patients with COVID-19 are at high risk of DDIs, mainly because of the drugs administered to treat SARS-CoV-2 infection. Remarkably, hospitalisation led an eightfold increase in

Table 3 Class D drug–drug interactions^a and potential adverse events upon hospital admission

Main DDIs	Potential adverse event	n (%)
Furosemide-induced DDI (n = 16)	Increased risk of cardiotoxicity (QT prolongation)	40 (87)
Amiodarone-induced DDI (n = 7)		
Quetiapine-induced DDI (n = 7)		
Formoterol-induced DDI (n = 5)		
Salmeterol-induced DDI (n = 5)		
Proton pump inhibitors + clopidogrel (n = 4)	Altered effect of antithrombotic therapy	4 (9)
Statin + vitamin K inhibitor (n = 1)	Increased risk of myopathy (rhabdomyolysis)	1 (2)
Proton pump inhibitor + methotrexate (n = 1)	Increased toxicity of methotrexate	1 (2)

^aContraindicated or very serious interaction associated with a serious event for which it is appropriate to avoid co-administration or establish careful monitoring

DDI drug–drug interaction

Table 4 Class D drug–drug interactions and potential adverse events during hospitalisation of patients with COVID-19

Main DDIs	Potential adverse event	n (%)
Lopinavir/ritonavir + hydroxychloroquine (n = 247)	Increased risk of cardiotoxicity (QT prolongation, Torsade de Pointes or life-threatening arrhythmias)	895 (88)
Lopinavir/ritonavir + azithromycin (n = 78)		
Lopinavir/ritonavir + piperacillin (n = 73)		
Other lopinavir/ritonavir-induced DDIs (n = 82)		
Hydroxychloroquine + piperacillin (n = 78)		
Hydroxychloroquine + azithromycin (n = 61)		
Other hydroxychloroquine-induced DDIs (n = 90)		
Other azithromycin-induced DDIs (n = 40)		
Other piperacillin-induced DDIs (n = 29)		
Lopinavir/ritonavir + statin (n = 38)		
Lopinavir/ritonavir + benzodiazepine (n = 14)	Depression of central nervous system respiratory functions	22 (2.2)
Lopinavir/ritonavir + benzodiazepine (n = 7)		
Lopinavir/ritonavir + DOACs (n = 14)	Altered effect of anti-thrombotic therapy	20 (2.0)
Proton pump inhibitors + clopidogrel (n = 4)		
Lopinavir/ritonavir + fluticasone (n = 10)	Increased systemic toxicity of corticosteroids (Cushing syndrome)	16 (1.6)
Lopinavir/ritonavir + budesonide (n = 4)		
Lopinavir/ritonavir + alfuzosin (n = 5)		
Lopinavir/ritonavir-induced DDI (n = 9)	Various	11 (1.1)
		16 (1.6)

COVID-19 coronavirus 2019 disease, DDI drug–drug interaction, DOACs direct oral anticoagulants

potentially severe DDIs involving drug combinations that should theoretically be avoided or managed by means of careful monitoring.

The most frequent potential adverse event was cardiac toxicity (increased risk of QT prolongation), which alone accounted for almost 90% of the predicted DDIs during hospitalisation. This is not unexpected because the cardiovascular safety of the drugs currently used to treat SARS-CoV-2 infection is still a subject of debate in the scientific community [13–15, 27–30]. Some of the concern is due to the observation that patients with COVID-19 are at increased risk of developing cardiovascular diseases regardless of treatment because the reported decrease in potassium levels can cause electrocardiographic changes such as a prolonged

QT interval [27–30]. Consequently, the administration of intrinsically cardiotoxic drugs such as hydroxychloroquine, lopinavir/ritonavir and/or azithromycin may further increase the risk of QT prolongation and potentially life-threatening arrhythmias in patients with COVID-19. Here, we found that nearly one-quarter of the class D DDIs observed in our study and potentially leading to cardiotoxicity could be unequivocally attributed to hydroxychloroquine. However, we feel that lopinavir/ritonavir is an even more relevant medication that has not received sufficient attention because, despite the growing and consistent evidence that it has a negative risk/benefit ratio, it is still being used to treat SARS-CoV-2 infection. The only published randomised clinical trial has clearly shown that it does not provide any significant advantage over

conventional therapy in hospitalised patients with COVID-19 [31]. Choy et al. [32] reported the *in vitro* inhibitory activity of lopinavir against SARS-CoV-2 virus in Vero E6 cells with an estimated 50% effective concentration at 26 μM . Accordingly, it has been estimated that the concentrations of lopinavir required to inhibit SARS-CoV-2 replication in plasma, epithelial lining fluid and cerebrospinal fluid are, respectively, 200, 20 and 2000 times higher than those measured *in vivo* in patients with COVID-19 [33–35], thus indicating that the lopinavir dose necessary to inhibit SARS-CoV-2 replication is clinically unachievable. Our findings show that >50% of the class D DDIs could be unequivocally attributed to lopinavir/ritonavir and that the cardiotoxicity risk ratio is double that of hydroxychloroquine and even greater than in other drugs said to be responsible for QT prolongation, such as azithromycin. Moreover, it must be considered that, according to the Credible Meds website, these drugs carry a different risk of QT prolongation: azithromycin and hydroxychloroquine are drugs with a known risk of QT prolongation, whereas lopinavir/ritonavir have a potential risk of cardiac toxicity, according to available literature. Taken together, these findings underline the complexity of the clinical relevance of a potentially severe DDI.

Lopinavir/ritonavir was also responsible for virtually all of the other potential DDIs leading to clinically highly relevant drug-related adverse events such as rhabdomyolysis, depressed central respiratory function or Cushing syndrome, as well as inadequate responses to anti-thrombotic and anti-hypertensive treatments. Taken together, these consequences argue that lopinavir has no place in the treatment of COVID-19, not only because of its unknown efficacy but also because of the unacceptably high risk of DDIs and drug toxicity.

It is worth noting that no clinically relevant DDIs were associated with the use of remdesivir and tocilizumab (two other drugs tested for SARS-CoV-2 infection) because, although this is not relevant in terms of efficacy, it is reassuring in terms of safety.

There was a dramatic increase in antibiotic consumption during hospitalisation that can only partially be explained by the use of azithromycin, which has been proposed as a treatment for SARS-CoV-2 infection because of its potential anti-viral and immunomodulatory properties [36]. Among the other antibiotics used because of clinical uncertainty or in patients with secondary bacterial infections, ceftriaxone and the carbapenems showed no potential for causing life-threatening DDIs. However, piperacillin/tazobactam were involved in some potentially severe DDIs associated with an increased risk of cardiotoxicity with the mechanism proposed being that piperacillin may cause a reduction in the potassium or magnesium serum concentrations. It must be acknowledged, however, that based on the Credible Meds website, piperacillin has a conditional risk for

QT prolongation; accordingly, the risk may become relevant only in the presence of bradycardia, low potassium or magnesium serum concentrations and/or use with concomitant drugs known to cause QT prolongation. These findings suggest that the potential for causing severe DDIs should be carefully considered when selecting antibiotic therapies.

Another interesting finding was that nearly half of the patients had at least one DDI at the time of admission, and one-quarter had at least one potentially severe DDI. The most frequent potential adverse event was, once again, an increased risk of cardiotoxicity due to DDIs involving various drug classes (diuretics, anti-asthmatics, anti-psychotics, and anti-arrhythmics).

Among the other potential adverse events, the large majority of class D DDIs were driven by proton pump inhibitors, thus indicating that, despite the information campaigns and other efforts to promote the correct use of this drug class, their potential for causing clinically relevant DDIs is still underestimated [37–39].

Half of the patients with COVID-19 enrolled in the study were aged >65 years, the threshold for assessing PIMs and the ACB established by consensus guidelines [15–17]. Using the updated Beers criteria, we found that the large majority of our patients had at least one PIM, with no difference between admission and hospitalisation. Although a detailed description of the rule violations is beyond the scope of this study, the fact that 95% of the elderly patients had at least one PIM upon admission clearly shows that general practitioners do not appropriately consider the problem of inappropriate drug prescriptions, and the fact that this percentage only marginally decreased to 88% during hospitalisation suggests that this is also true of hospital physicians. It is possible that physicians are not sufficiently aware of the available means of optimising drug prescriptions, although it may be that the severity of the clinical condition of some patients with COVID-19 obliged them to accept the risk of serious DDIs.

Only 3% of our patients with COVID-19 had an ACB score of ≥ 5 , which may reflect physicians' greater awareness of the risks associated with the cumulative effect of anti-cholinergic drugs or that our population mainly consisted of younger elderly patients or elderly patients with a low incidence of co-morbidities requiring treatment with anti-cholinergic drugs. In any case, the treatment of SARS-CoV-2 infection had no impact on ACB scores.

The main limitation of our study was that no outcome data (i.e. mortality, length of stay) were available. This study was not designed or powered to assess the impact of DDIs, PIMs and/or ACB on the clinical outcomes of the enrolled patients, but we are confident that its findings provide a rationale for the more balanced management of patients with COVID-19, at least in terms of pharmacological burden. An additional limitation was that the present study was not

designed or powered to assess properly the impact of aging on the polypharmacy burden and the risk of DDIs in patients with COVID-19. However, it must be considered that 50% of the enrolled patients were aged > 65 years. Accordingly, it would be reasonable to speculate that the potential DDIs described in the present study would have an impact on a proportion of elderly people with COVID-19.

Finally, it is important to underline that this study provides a snapshot of the situation of COVID-19 at the beginning of the pandemic. The scenario is constantly changing, so potential DDIs involving remdesivir, corticosteroids and anticoagulants should be considered. According to available literature, the risk of pharmacokinetic- and pharmacodynamic-based DDIs is low for remdesivir [40, 41]. However, since this drug is a substrate of cytochromes 3A4, 2D6, and 2C8, the potential co-administration of inhibitors can lead to a potential increase in remdesivir levels. Therefore, as we deal with critically ill patients with COVID-19 with underlying co-morbidities, clinicians need to be careful about co-administering drugs with remdesivir and be updated regularly as new data emerge [42]. More DDIs are expected for corticosteroids [43] and direct oral anticoagulants often used in place of enoxaparin [44].

5 Conclusions

Concomitant treatment with hydroxychloroquine and lopinavir/ritonavir in hospitalised patients with COVID-19 led to a dramatic increase in the number of potentially severe DDIs. Given the consequently high risk of cardiotoxicity and the conflicting data concerning their potential efficacy in treating SARS-CoV-2 infection, the use of lopinavir/ritonavir and hydroxychloroquine in patients with COVID-19 with polypharmacy needs to be carefully evaluated. Computerised prescription support systems (and possibly multidisciplinary teams of healthcare providers with expertise in the field, such as infectious disease physicians, pharmacologists, hospital pharmacists and cardiologists) should be widely adopted by all hospitals involved in the management of patients with COVID-19 to assess the appropriateness of drug prescriptions.

Declarations

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Conflict of interest DC, LP, APM, AG, LO, AC, LB, MS, SA, AR, and CG have no conflicts of interest that are directly relevant to the content of this article. CG has received personal fees from MSD, ViiV, Gilead and Janssen Cilag unrelated to this study. DC has received personal fees from MSD, ViiV, and Janssen Cilag unrelated to this study. APM has received personal fees from Bayer, Fresenius, and Novartis for participating in study committees unrelated to this study.

Ethics approval The study was approved by our hospital's ethics committee (Comitato Etico Interaziendale Area 1).

Consent All of the patients included in the study signed an informed consent form for the administration of off-label treatments.

Availability of data and material The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions Research design and manuscript first draft: DC, CG. Provision of study materials or patients: AG, AC, LB, MS, SA, AR, CG. Data analysis: DC, LP, APM, and LO. Final manuscript approval: all authors.

References

1. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med.* 2020;108:934.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395:1054–62.
3. Liu X, Zhou H, Zhou Y, Wu X, Zhao Y, Lu Y, et al. Risk factors associated with disease severity and length of hospital stay in COVID-19 patients. *J Infect.* 2020;81:e95–7.
4. Chary A, Nguyen NN, Maiton K, Holodniy M. A review of drug-drug interactions in older HIV-infected patients. *Expert Rev Clin Pharmacol.* 2017;10:1329–52.
5. Pasqualetti G, Tognini S, Calsolaro V, Polini A, Monzani F. Potential drug-drug interactions in Alzheimer patients with behavioral symptoms. *Clin Interv Aging.* 2015;10:1457–66.
6. Petrini E, Caviglia GP, Pellicano R, Saracco GM, Morino M, Ribaldone DG. Risk of drug interactions and prescription appropriateness in elderly patients. *Ir J Med Sci.* 2019;189:953–9.
7. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol.* 2003;38:843–53.
8. Thürmann PA. Pharmacodynamics and pharmacokinetics in older adults. *Curr Opin Anaesthesiol.* 2020;33:109–13.
9. Back D, Marzolini C. The challenge of HIV treatment in an era of polypharmacy. *J Int AIDS Soc.* 2020;23:e25449.
10. Mannucci PM, Nobili A, Pasina L, REPOSI Collaborators. Polypharmacy in older people: lessons from 10 years of experience with the REPOSI register. *Intern Emerg Med.* 2018;13:1191–200.
11. Abolbashari M, Macaulay TE, Wayne TF, Mukherjee D, Saha S. Polypharmacy in cardiovascular medicine: problems and promises! *Cardiovasc Hematol Agents Med Chem.* 2017;15:31–9.
12. Cattaneo D, Cossu MV, Rizzardini G. Pharmacokinetic drug evaluation of ritonavir (versus cobicistat) as adjunctive therapy in the treatment of HIV. *Expert Opin Drug Metab Toxicol.* 2019;15:927–35.
13. Saleh M, Gabriels J, Chang D, Kim BS, Mansoor A, Mahmood E, et al. The effect of chloroquine, hydroxychloroquine and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. *Circ Arrhythm Electrophysiol.* 2020 (**Epub ahead of print**).
14. Mercurio 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.

15. Javelot H, El-Hage W, Meyer G, Becker G, Michel B, Hingray C. COVID-19 and (hydroxy)chloroquine-azithromycin combination: Should we take the risk for our patients? *Br J Clin Pharmacol*. 2020;86:1176–7.
16. Baumgartner AD, Clark CM, LaValley SA, Monte SV, Wahler RG Jr, Singh R. Interventions to deprescribe potentially inappropriate medications in the elderly: lost in translation? *J Clin Pharm Ther*. 2020;45:453–61.
17. Monteiro L, Maricoto T, Solha I, Ribeiro-Vaz I, Martins C, Monteiro-Soares M. Reducing potentially inappropriate prescriptions for older patients using computerized decision support tools: systematic review. *J Med Internet Res*. 2019;21:e15385.
18. Vrdoljak D, Borovac JA. Medication in the elderly—considerations and therapy prescription guidelines. *Acta Med Acad*. 2015;44:159–68.
19. Cooper JA, Cadogan CA, Patterson SM, Kerse N, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. *BMJ Open*. 2015;5:e009235.
20. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatr*. 2015;15:31–41.
21. Martocchia A, Spuntarelli V, Aiello F, Meccariello AL, Proietta M, Del Porto F, et al. Using INTERCheck® to evaluate the incidence of adverse events and drug-drug interactions in out- and inpatients exposed to polypharmacy. *Drugs Real World Outcomes*. 2020;7:243–9.
22. Ghibelli S, Marengoni A, Djade CD, Nobili A, Tettamanti M, Franchi C, et al. Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck®). *Drugs Aging*. 2013;30:821–8.
23. Pasina L, Marengoni A, Ghibelli S, Suardi F, Djade CD, Nobili A, et al. A multicomponent intervention to optimize psychotropic drug prescription in elderly nursing home residents: an Italian multicenter, prospective, pilot study. *Drugs Aging*. 2016;33:143–9.
24. Antoniazzi S, Chiarelli MT, Nobili A, Pasina L, Venturini F. The value of software that provides clinically relevant information on drug interactions. *Eur J Intern Med*. 2015;26:e52–3.
25. Pasina L, Novella A, Cortesi L, Nobili A, Tettamanti M, Ianes A. Drug prescriptions in nursing home residents: an Italian multicenter observational study. *Eur J Clin Pharmacol*. 2020;76:1011–9.
26. Chiarelli MT, Antoniazzi S, Cortesi L, Pasina L, Novella A, Venturini F, et al. Pharmacist-driven medication recognition/reconciliation in older medical patients. *Eur J Intern Med*. 2020;S0953–6205:30294–6.
27. Aggarwal G, Henry BM, Aggarwal S, Bangalore S. Cardiovascular safety of potential drugs for the treatment of coronavirus disease 2019. *Am J Cardiol*. 2020;128:147–50.
28. Aggarwal G, Cheruiyot I, Aggarwal S, Wong J, Lippi G, Lavie CJ, et al. Association of cardiovascular disease with coronavirus disease 2019 (COVID-19) severity: a meta-analysis. *Curr Probl Cardiol*. 2020;45:100617.
29. Gérard A, Romani S, Fresse A, Viard D, Parassol N, Granvillain A, et al. “Off-label” use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: a survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapie*. 2020;75:371–9.
30. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review. *Heart Rhythm*. 2020;S1547–5271:30431–8.
31. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382:1787–99.
32. Choy KT, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res*. 2020;178:104786.
33. Cattaneo D, Corbellino M, Galli M, Riva A, Clementi E, Gervasoni C. Does lopinavir really inhibit SARS-CoV-2? *Pharmacol Res*. 2020;158:104898.
34. Smith PF, Dodds M, Bentley D, Yeo K, Rayner C. Dosing will be a key success factor in repurposing antivirals for COVID-19. *Br J Clin Pharmacol*. 2020 (**Epub ahead of print**).
35. Schoergenhofer C, Jilma B, Stimpfl T, Karolyi M, Zoufaly A. Pharmacokinetic of lopinavir and ritonavir in patients hospitalized with coronavirus disease 2019 (COVID-19). *Ann Intern Med*. 2020;173:670–2.
36. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56:105949.
37. Schnoll-Sussman F, Niec R, Katz PO. Proton pump inhibitors: the good, bad, and ugly. *Gastrointest Endosc Clin N Am*. 2020;30:239–51.
38. Wang X, Song Y, Wang J, He J, Liu R, Li X, et al. Effect of proton pump inhibitors on high-dose methotrexate elimination: a systematic review and meta-analysis. *Int J Clin Pharm*. 2020;42:23–33.
39. Kanno T, Moayyedi P. Proton pump inhibitors in the elderly, balancing risk and benefit: an age-old problem. *Curr Gastroenterol Rep*. 2019;21:65.
40. Gandhi Z, Mansuri Z, Bansod S. Potential interactions of remdesivir with pulmonary drugs: a Covid-19 perspective. *SN Compr Clin Med*. 2020;2:1707–8.
41. Yang K. What Do we know about remdesivir drug interactions? *Clin Transl Sci*. 2020;13:842–4.
42. Leegwater E, Strik A, Wilms EB, Bosma LBE, Burger DM, Ottens TH, van Nieuwkoop C. Drug-induced liver injury in a COVID-19 patient: potential interaction of remdesivir with P-glycoprotein inhibitors. *Clin Infect Dis*. 2020 (**Epub ahead of print**).
43. Ferràu F, Ceccato F, Cannavò S, Scaroni C. What we have to know about corticosteroids use during Sars-Cov-2 infection. *J Endocrinol Invest*. 2020 (**Epub ahead of print**).
44. Ghasemiyeh P, Borhani-Haghighi A, Karimzadeh I, Mohammadi-Samani S, Vazin A, Safari A, et al. Major neurologic adverse drug reactions, potential drug-drug interactions and pharmacokinetic aspects of drugs used in covid-19 patients with stroke: a narrative review. *Ther Clin Risk Manag*. 2020;16:595–605.