



Drug–Drug Interactions and Prescription Appropriateness at Hospital Discharge: Experience with COVID-19 Patients

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Accepted: 28 January 2021 / Published online: 1 March 2021
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Abstract

Background Patients with coronavirus disease 2019 (COVID-19) are often elderly, with comorbidities, and receiving polypharmacy, all of which are known factors for potentially severe drug–drug interactions (DDIs) and the prescription of potentially inappropriate medications (PIMs).

Objective The aim of this study was to assess the risk of DDIs and PIMs in COVID-19 patients at hospital discharge.

Method Patients with a proven diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were hospitalized between 21 February and 30 April 2020, treated with at least two drugs, and with available information regarding pharmacological treatments upon admission and at discharge were considered. The appropriateness of drug prescriptions was assessed using INTERcheck[®].

Results A significant increase in the prescription of proton pump inhibitors and heparins was found when comparing admission with hospital discharge (from 24 to 33% [$p < 0.05$] and from 1 to 17% [$p < 0.01$], respectively). The increased prescription of heparins at discharge resulted in a highly significant increase in the potentially severe DDIs mediated by this class of drugs. 51% of COVID-19 patients aged > 65 years had at least one PIM upon admission, with an insignificant increment at discharge (58%).

Conclusion An increased number of prescribed drugs was observed in COVID-19 patients discharged from our hospital. The addition of heparins is appropriate according to the current literature, while the use of proton pump inhibitors is more controversial. Particular attention should be paid to the risk of bleeding complications linked to heparin-based DDIs.

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Key Points

A significant increase in the prescription of proton pump inhibitors and heparins was found in COVID-19 patients when comparing hospital admission with discharge.

The increased prescription of heparins at discharge resulted in a highly significant increase in the potentially severe drug–drug interactions mediated by this class of drugs.

More than 50% of COVID-19 patients aged > 65 years had at least one potentially inappropriate medication at both admission and discharge.

1 Introduction

It has been estimated that up to 50% of patients with coronavirus disease 2019 (COVID-19) have at least one comorbidity [1]. This is a clinically relevant issue as comorbidities have been identified as key factors associated with a negative prognosis in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2, 3]. Another prominent risk factor for severe disease and death from COVID-19 is aging [4, 5]. It has been hypothesized that age-related decline and dysregulation of immune function play a major role in contributing to heightened vulnerability to severe COVID-19 outcomes in older adults [5].

A high rate of polypharmacy for the treatment of existing aging-related chronic disease conditions is expected in this population [6, 7]. The polypharmacy burden is likely to be increased in hospitalized COVID-19 patients by the addition of specific treatments for SARS-CoV-2 infection. Accordingly, it has been previously reported that the use of lopinavir/ritonavir, hydroxychloroquine, and/or azithromycin resulted in clinically relevant drug–drug interactions (DDIs) [1]. Furthermore, 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 COVID-19 patients at extremely high risk for the prescription of potentially inappropriate medications (PIMs) and experiencing potentially severe DDIs.

In the past few years, great efforts have been made in the search for interventions to improve the appropriateness of prescriptions in patients with multiple comorbid diseases. The various computerized 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 anticholinergic burden (ACB) [8, 9]. We have recently demonstrated that more than 50% of patients with COVID-19 were treated with at least one PIM and were exposed to at least one potential DDI, and the proportion of patients experiencing a potentially severe DDI increased significantly from 20% at admission to 80% during hospitalization [10]. In this report, we aim to extend the previous findings by assessing the risk of potentially severe DDIs and PIMs in COVID-19 patients at hospital discharge.

2 Methods

We searched the database of the Department of Infectious Diseases of Luigi Sacco Hospital (Milan, Italy) for patients with a proven diagnosis of SARS-CoV-2 infection (a throat

swab positive for viral nucleic acid) who were hospitalized between 21 February and 30 April 2020, treated with at least two drugs, and with available information regarding pharmacological treatments on admission and discharge. The appropriateness of drug prescriptions was assessed using INTERcheck[®], a Computerized Prescription Support System that classifies 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); and minor (A, drug combinations with no known clinical relevance) [10]. In the present study, we considered only potentially severe DDIs, defined as the sum of class D and class C DDIs [10]. PIMs were defined using Beers criteria [8]. The ACB was investigated using as threshold value ≥ 3 , indicating a risk of adverse events [9]. DDIs were assessed in all COVID-19 patients, whereas PIMs (through the application of the Beers criteria) and the ACB were only assessed in those aged > 65 years. The study was approved by our hospital's Ethics Committee (Comitato Etico Interaziendale Area 1).

The frequency distribution data are expressed as absolute numbers and percentages, while all other measures are expressed as mean values \pm standard deviations. Differences in the risk of DDIs, PIMs, and ACB score upon admission and at discharge were tested using Student's *t* test for continuous variables and Pearson's Chi-square test for dichotomous and unordered categorical data.

3 Results

Overall, 201 patients fulfilling the inclusion criteria were identified from 502 hospitalized COVID-19 patients. Male sex predominated (64%) and mean age was 63 ± 13 years. At the time of admission, patients received 3.5 ± 2.8 drugs, with the number of drugs increasing at discharge to 4.0 ± 3.0 ($p = 0.057$). As shown in Table 1, the most frequently prescribed drugs were antihypertensive agents (mainly angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers and β -blockers), diuretics, hypoglycemic agents, and statins, with no significant differences between admission and discharge. Conversely, a significant increase in the prescription of proton pump inhibitors (PPIs) and heparins (almost exclusively enoxaparin) was found between the two observational periods (from 24 to 33% [$p < 0.05$] and from 1 to 17% [$p < 0.01$], respectively). As potential COVID-19 treatment, during hospitalization, patients received hydroxychloroquine (87%), lopinavir/ritonavir (70%), corticosteroids (33%), tocilizumab (24%), remdesivir

Table 1 Pharmacologic burden of COVID-19 patients at admission to the hospital versus discharge

| Clinical features | Admission | Discharge |
|---|-----------|------------------|
| Patients, <i>n</i> | 201 | 198 ^a |
| Age, years [mean (SD)] | 63 ± 13 | 63 ± 13 |
| Women | 73 (36) | 73 (37) |
| Mean number of drugs (%) [mean (SD)] | 3.5 ± 2.8 | 4.0 ± 3.0 |
| Most frequently used drugs ^b | | |
| ACE inhibitors/angiotensin receptor blockers | 79 (39) | 73 (37) |
| Proton pump inhibitors | 48 (24) | 66 (33)* |
| β-blockers | 47 (23) | 47 (24) |
| Diuretics | 45 (22) | 43 (22) |
| Hypoglycemic agents | 42 (21) | 52 (26) |
| Calcium channel blockers | 37 (18) | 36 (18) |
| Statins | 36 (18) | 33 (17) |
| Vitamins | 28 (14) | 35 (18) |
| Psychotropic drugs | 27 (13) | 34 (17) |
| Heparins | 3 (1) | 34 (17)** |
| Patients with at least one DDI | 87 (43) | 92 (46) |
| Patients with at least one potentially severe DDI | 40 (20) | 49 (25) |
| Heparin-induced potentially severe DDI | 1 (0.5) | 11 (6)** |
| Patients aged >65 years | 90 (45) | 88 (44) |
| Patients with at least one PIM | 103 (51) | 115 (58) |
| Patients with an ACB score ≥3 | 13 (6) | 14 (7) |

Data are expressed as *n* (%) unless otherwise specified

COVID-19 coronavirus disease 2019, DDI drug–drug interaction, ACE angiotensin-converting enzyme, PIM potentially inappropriate medication according to the Beers criteria, ACB anticholinergic burden, * *p* < 0.05 and ** *p* < 0.01 vs. admission

^aThree patients died

^bSome patients were administered more than 1 drug

(19%), and/or azithromycin (13%) [data on potential DDIs and PIMs during hospitalization have already been described elsewhere] [10]).

At admission, 43% of enrolled patients were exposed to at least one potential DDI, 20% of which were classified as potentially severe. These percentages did not change significantly at discharge (46% and 25%, respectively) [Table 1]. The same trend was also observed when clustering the potentially severe DDIs according to the type of adverse event (Table 2). The main drivers of the DDIs were the diuretic furosemide, the antiarrhythmic amiodarone, acetylsalicylic acid, and antihypertensive calcium channel blockers. Remarkably, the observed increased prescription of heparins at discharge resulted in a highly significant increase in the potentially severe DDIs. Specifically, 1 potentially severe DDI (increased risk of bleeding related to the coadministration of enoxaparin with acetylsalicylic acid) at admission versus 11 potentially severe DDIs at discharge were

Table 2 Class C (major: drug combinations requiring close monitoring for potentially serious clinical consequences, such as severe adverse effects or lack of clinical efficacy) and class D (contraindicated: drug combinations that should be avoided) drug–drug interactions and potential adverse events of COVID-19 patients at admission versus discharge to the hospital

| Severe DDIs and their main perpetrators | Admission | Discharge |
|---|-----------|-----------|
| No. of potentially severe DDIs | 96 | 109 |
| Increased risk of cardiotoxicity | 30 (31%) | 32 (29%) |
| Amiodarone-induced DDIs | 7 | 8 |
| Furosemide-induced DDIs | 7 | 7 |
| Proton pump inhibitor-induced DDIs | 3 | 3 |
| Promazine-induced DDIs | 3 | 4 |
| Trazodone-induced DDIs | 3 | 3 |
| Others | 7 | 7 |
| Altered effect of antithrombotic therapy | 18 (19%) | 28 (27%) |
| Acetylsalicylic acid-induced DDIs | 5 | 13 |
| SSRI-induced DDIs | 4 | 7 |
| Amiodarone-induced DDIs | 3 | 1 |
| Proton pump inhibitor-induced DDIs | 2 | 2 |
| Others | 4 | 5 |
| Increased risk of myopathy (rhabdomyolysis) | 15 (15%) | 11 (10%) |
| CCB-induced DDIs | 6 | 7 |
| Vitamin K inhibitor-induced DDIs | 4 | 1 |
| Fibrate-induced DDIs | 2 | 2 |
| Others | 3 | 1 |
| Increased risk of hypoglycemia | 7 (7%) | 3 (3%) |
| Insulin + metformin | 4 | 2 |
| Others | 3 | 1 |
| Electrolyte disorders | 6 (6%) | 9 (8%) |
| SSRI-induced DDIs | 4 | 5 |
| Others | 2 | 4 |
| Depression of CNS respiratory function | 6 (6%) | 8 (7%) |
| Opioid-induced DDIs | 4 | 6 |
| β-agonist-induced DDIs | 2 | 2 |
| Others | 14 (15%) | 18 (17%) |

DDI drug–drug interaction, SSRI selective serotonin reuptake inhibitors, CCB calcium channel blockers, CNS central nervous system

recorded. The latter were associated with an increased risk of bleeding related to the coadministration of enoxaparin with acetylsalicylic acid (*n* = 6), warfarin (*n* = 2) or escitalopram (*n* = 1), and an increased risk of hyperkalemia (*n* = 2) related to the coadministration of enoxaparin with spironolactone.

Forty-five percent of patients with COVID-19 were aged >65 years. Actually 50% of them had at least one PIM upon admission on the basis of the updated Beers criteria, with no significant increment at discharge (58%). ACB scores ≥3 were recorded in 6% and 7% of patients, with no significant difference between admission and discharge, respectively (Table 1).

4 Discussion

This study shows a trend for a higher number of prescribed drugs in COVID-19 patients discharged from our hospital, when compared with admission. This was mainly driven by two classes of drugs, namely heparins and PPIs. The role of heparins in the prevention and treatment of thromboembolic complications of COVID-19 has been widely established [11, 12]. In a prospective, observational study involving 315 patients with laboratory-confirmed SARS-CoV-2 pneumonia, Falcone et al. have shown that low-molecular-weight heparins (LMWHs) significantly reduced the risk of in-hospital mortality and severe acute respiratory distress syndrome [13]. Similarly, a nationwide cohort study of 4297 hospitalized patients in the US provided evidence that early initiation of prophylactic anticoagulation among patients hospitalized with COVID-19 was associated with a decreased risk of mortality [14]. More recently, it has also been proposed that LMWHs may be useful in modulating the COVID-19-related cytokine storm and in counteracting the entry of SARS-CoV-2 into the cells [11, 12]. The observed significant increase in the prescription of heparins at patient discharge is therefore expected and is supported by the available literature [11–14]. However, it must be remembered that this class of drugs is not devoid from potentially severe DDIs. In particular, a high risk of bleeding has been reported when enoxaparin was combined with acetylsalicylic acid or oral anticoagulants [15, 16]. In agreement with these findings, the potentially serious DDIs identified by the INTERCHECK[®] software in our study related mainly to the associations between enoxaparin and acetylsalicylic acid or warfarin, highlighting the importance of carefully evaluating overall antithrombotic therapy in COVID-19 patients prior to hospital discharge. Direct oral anticoagulants could be a feasible alternative to heparins for COVID-19 patients at risk of DDIs with heparins; however, potentially serious DDIs also involving new oral anticoagulants have been described in the setting of COVID-19 [17, 18].

Beside heparins, the only other class for which there was a significant increase in prescriptions at the time of discharge was PPIs. To the best of our knowledge, no studies have been published to date demonstrating a key role of this drug class in the management of COVID-19 patients. Instead, we believe that despite information campaigns (either within the hospital and in the community) and other efforts to promote the correct use of PPIs, overuse remains excessive and their potential for causing clinically relevant DDIs is still underestimated [19]. We hypothesized that PPIs were prescribed at hospital discharge to provide gastrointestinal protection, given the high number

of drugs started during hospital stay and eventually continued thereafter. The use/abuse of PPIs is likely to increase further following recent recommendations for corticosteroids in COVID pneumonia [20, 21]. Beside their potential to cause DDIs, patients taking PPIs (eventually also during prehospitalization) are at increased risk for worse clinical outcomes, including the development of ventilator-associated pneumonia and/or mortality, in COVID-19 patients, regardless of the presence of cardiovascular morbidities [22, 23].

One of the other findings from our study is that the number and frequency of PIMs did not change significantly when comparing admission versus discharge. We believe that this result can be interpreted in two opposing ways. This might be either a reassuring message for patients that the large majority of potentially severe DDIs and PIMs reported during hospital stay [10] and mainly related to the use of lopinavir/ritonavir and/or hydroxychloroquine and/or azithromycin were no longer present at discharge, suggesting that physicians have carefully evaluated and balanced the advantages and risks of these drug combinations. On the other hand, the fact that 50% and 20% of the COVID-19 patients had at least one PIM and at least one potentially severe DDI, respectively, at hospital discharge suggests that an overall assessment of the appropriateness of all pharmacologic treatments, including background therapies, was not performed adequately during the hospital stay; however, this could be understandable in an emergency situation such as that caused by COVID-19.

5 Conclusions

An increase in prescribed drugs was observed in COVID-19 patients discharged from our hospital. This trend was mainly driven by the addition of PPIs and/or heparins to the background therapies recorded at patient admission. The addition of heparins is appropriate according to the current literature, while the use of PPIs is more controversial. Both classes of drugs increased the risk of potentially severe DDIs. Particular attention should be paid to the risk of bleeding linked to heparin-based DDIs. Computerized prescription support systems should be widely adopted by all hospitals involved in the management of patients with polypharmacy in order to assess the suitability of drug prescriptions.

Declarations

Funding Open access funding provided by Università degli Studi di Milano within the CRUI-CARE Agreement.

Conflict of interest All authors declare no competing interests for the present study. Cristina Gervasoni has received personal fees from

MSD, ViiV, Gilead and Jansen Cilag unrelated to this study. Dario Cattaneo has received personal fees from MSD, ViiV, and Jansen Cilag unrelated to this study. Aldo Pietro Maggioni has received personal fees from Bayer, Fresenius, and Novartis for participating in study committees unrelated to this study. Luca Pasina, Letizia Oreni, Federico Conti, Laura Pezzati, Giacomo Casalini, Cecilia Bonazzetti, Valentina Morena, Annalisa Ridolfo, and Spinello Antinori declare they have no potential conflicts of interest.

Ethics approval This study was approved by the Ethics Committee (Comitato Etico Interaziendale Area 1) at our hospital.

Consent to participate All patients included in this study signed an informed consent form.

Consent for publication Not applicable.

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

Code availability Not applicable.

Author contributions Research design and manuscript first draft: DC, CG. Provision of study materials or patients: FC, LP, GC, CB, VM, AR, SA, CG. Data analysis: DC, LP, APM, and LO. Final manuscript approval: All authors.

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