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# High Prevalence of Potential Drug-Drug Interactions among Patients Treated with off-Label Therapies for COVID-19

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ABSTRACT

***Background:*** During the first wave of the COVID-19 pandemic, severe patients were treated with the off-label drugs hydroxychloroquine and lopinavir/ritonavir. The aim of the study was to determine the prevalence of potential drug-drug interactions (DDIs) between hydroxychloroquine, lopinavir/ritonavir and concomitant medications used by hospitalized patients treated for COVID-19 in Costa Rica.

***Methods:*** We included all patients that received lopinavir/ritonavir or hydroxychloroquine as treatment for COVID-19. Clinical pharmacists reviewed the prescription profile of each patient and determined the probability and severity of any DDI through two databases (The Lexi-Interact program) and the Micromedex online interaction checker. A logistic regression model was used to identify variables associated with the occurrence of potential DDIs.

***Results:*** We identified a total of 108 potential DDIs in 34 inpatients (n=34). At least one of these DDIs occurred in 27 patients (79.4%; 95% CI: 65.8-92.9%). A total of 70 DDIs (64.8%) were classified as clinically relevant (grade D or X) by the clinical pharmacists. Only the number of concomitant drugs was associated with the occurrence of a probable DDI. The most common drugs associated with any DDI were fentanyl (n=12, 11.1%), midazolam (n=11, 10.2%), and insulin (n=10, 10.2%).

***Conclusion:*** A large proportion of patients treated with hydroxychloroquine and lopinavir/ritonavir for severe COVID-19 were at risk for clinical meaningful DDIs.

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## Introduction

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently a major global problem (1). Although the majority of patients experience mild or moderate disease, severe cases usually need hospitalization, intensive care, and assisted mechanical ventilation (2). At the beginning of this pandemic, due to the scarce data of effective antiviral treatments, use of off-label drugs was recommended by some Institutions (3). Antiviral drugs such as lopinavir and ritonavir, and antimalarial drugs such as chloroquine and hydroxychloroquine were urgently administered to patients with COVID-19 based on pre-clinical and clinical data (4-6). Although, these drugs are not currently recommended for patients with COVID-19, they were broadly used at the beginning of

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this pandemic (7). Despite the potential antiviral activity of these drugs, they are well-known to be implicated in drug-drug interactions (DDIs), especially in severe hospitalized patients who are treated with a large variety of therapies for their current infection and for pre-existing comorbidities.

A drug interaction is defined as "the pharmacological response to the administration or co-exposure of a drug with another substance that modifies the patient's response to that drug." (8). DDIs are classified either as pharmacodynamics or pharmacokinetic depending on the underlying mechanism of action (9). Pharmacodynamics DDIs occur when the concomitant drug antagonizes or potentiates the pharmacological effect of the other substance resulting in an inhibitory or additive effect, respectively. On the other hand, pharmacokinetic DDIs occur when the concomitant drug alters the absorption, distribution, metabolism, or excretion of the other substance. These interactions are frequently associated with serious adverse events as result of changes on the toxicity of the associated treatment, particularly in patients with serious illness and underlying diseases. To our knowledge few reports have quantified the amount and severity of DDIs among COVID-19 patients treated with unapproved therapies (10,11). Indeed, most of the published reports have focused on clinical cases or warnings from regulatory agencies (12-14).

In this study we hypothesized that hospitalized COVID-19 patients treated with the off-label therapies lopinavir/ritonavir and hydroxychloroquine were at high risk of developing clinically significant DDIs. The aim of this retrospective study was to quantify and classify the potential DDIs among inpatients exposed to these drugs in three major hospitals in Costa Rica from March to July 2020.

## Methods

A cross-sectional study was conducted with inpatients admitted to the three major hospitals in San José, Costa Rica (Hospital Rafael Angel Calderón Guardia, Hospital México, and Hospital San Juan de Dios, Caja Costarricense de Seguro Social). We included all hospitalized patients that received lopinavir/ritonavir or hydroxychloroquine as treatment for COVID-19. All COVID-19 cases were confirmed by polymerase chain reaction (PCR) test according to the WHO criteria (15). We excluded patients with previous use of hydroxychloroquine or lopinavir/ritonavir. The Ethics Committee of the Caja Costarricense de Seguro Social (CEC-CENDEISSS) approved the protocol of this study (Protocol No. R020-SABI-00256).

Patients were identified from the computer-based medication prescription system of each hospital pharmacy. Due to the recommendation of the WHO and other Regulatory Agencies, patients were not considered candidates for these treatments as from July 2020. Therefore, we only included patients from March 2020 to July 2020. All data were retrieved retrospectively in September 2020.

To maximize the detection of potential DDIs potential DDIs were identified through two databases (The Lexi-Interact program, available at: http://webstore.lexi.com/Store/Individual-Databases/Lexi-Interact and the online interaction checker provided by Micromedex, available at: http://www.knowledge.scot.nhs.uk/home.aspx). Interactions found in both databases were only counted once. Drug formulations containing two or more pharmacologically active ingredients were counted individually in the analysis. Each potential interaction was classified by the clinical pharmacist as pharmacodynamic or pharmacokinetic depending on the underlying mechanism of action. The severity of each potential DDI was categorized as clinically relevant if they were classified as D ("consider therapy modification"), or X ("avoid combination") according to the Lexi-Interact software.

Categorical variables are presented as percentages, and continuous variables as means and standard deviations. A univariate binomial logistic regression analysis was performed to identify potential variables associated with the occurrence of any potential DDI. The variables included in this model were: sex, age, number of concomitant drugs and number of comorbidities. Those variables with a p value less than 0.10 after the univariate analysis were included in a multivariate stepwise logistic regression approach. A p value less than 0.05 was considered statistically significant. All statistical procedures were performed with SPSS 21.1 for Mac (Chicago Il, USA).

## Results

During the study timeframe we identified 34 inpatients who met the inclusion criteria. The majority of the patients were male (n=24, 70.5%) with a mean age of 58.7 ± 13.6 years (range: 31-85 years). The most common comorbidities were hypertension (n=19, 55.9%), followed by diabetes mellitus (n=10, 29.4%), cancer and cardiopathies (n=7 both, 20.6%), and chronic obstructive pulmonary disease

(n=3, 8.8%). The most common reason for hospitalization was severe sepsis (n=17, 50%) followed by respiratory failure (n=10, 29.4%). The mean number of concomitant drugs used in combination with hydroxychloroquine or lopinavir/ritonavir was 12 (range: 1 to 31).

After reviewing 671 drug combinations employed by the included patients during their hospitalization, we detected 108 potential DDIs between hydroxychloroquine or lopinavir/ritonavir and other concomitant medications. At least one of these DDIs occurred in 27 patients (79.4%; 95% CI: 65.8-92.9%). The most frequent mechanism of interaction was pharmacokinetic in 69 cases (63.8%), specifically due to impaired metabolism of the concomitant drug (n=65) followed by altered drug absorption in 3 cases. A total of 19 pharmacodynamic interactions (17.6%) were associated with potential QT interval prolongation.

The most common drugs associated with any DDI were fentanyl (n=12, 11.1%), midazolam (n=11, 10.2%), insulin (n=10, 10.2%), clarithromycin (n=8, 7.4%), amiodarone (n=7, 6.5%), and omeprazole (n=7, 6.5%).

A total of 70 DDIs (64.8%) were classified as clinically relevant (grade D or X) by the clinical pharmacist. The supplementary appendix provides a resumed list of the mechanism and severity of the more frequent and clinically relevant DDIs found in our data set.

The results of the univariate regression model are shown in Table 1. Only the number of concomitant drugs was significantly associated with the occurrence of any DDI. Since no other variables were associated with this outcome, we did not perform the multivariate analysis.

**Table 1.** Univariate regression analysis of variables associated with the occurrence of any drug-drug interaction.

| Variable | Univariate odds ratio (95% Confidence Interval) | p value |
|---|---|---|
| Age | 1.03 (0.94 – 1.06) | 0.92 |
| Male sex | 0.61 (0.12 – 3.27) | 0.61 |
| Number of concomitant drugs | 1.20 (1.01 – 1.41) | 0.03 |
| Number of comorbidities | 1.54 (0.81 – 2.93) | 0.18 |

## Discussion

Our findings showed a high prevalence of potential DDIs among hospitalized patients treated with the unapproved therapies hydroxychloroquine and lopinavir/ritonavir for severe COVID-19. Although these drugs are no longer recommended due to the lack of consistent clinical benefit in randomized clinical trials, (16-19) the results of this retrospective study should aware the medical community about the potential serious clinical consequences of using these drugs in severely ill patients. More importantly is the fact of avoiding the use of off-label therapies in COVID-19 patients based on small clinical trials with discordant results.

According to our data, a high proportion of patients were at risk for clinically relevant DDIs that could lead to serious side effects such as arrhythmias, respiratory depression, severe hypoglycemia, and rhabdomyolysis. Indeed, these potential DDIs have been alerted by previous authors and medical societies raising concerns regarding the safety profile of these drugs (12-14, 20).

Although previous studies have alerted the possible occurrence of DDIs among hospitalized patients with COVID-19 and concomitant use of hydroxychloroquine or lopinavir/ritonavir, few authors have reported the actual rate of these potential DDIs and their clinical consequences. Such studies have reported a high proportion of inpatients with potential DDIs ranging from 62 (21,22) to 87% (10,23). Besides, these studies found that the majority of potential DDIs were due to the concomitant use of either hydroxychloroquine or lopinavir/ritonavir. Our findings, as well as previous reports, coincide on the high frequency of DDIs among hospitalized patients, especially among those patients with severe disease and respiratory support. However, in contrast with previous reports, our dataset was mainly composed of younger patients with less comorbidities at baseline, highlighting the fact that these interactions can occur in patients with no classical risk factors for DDIs.

As expected, our analysis showed that patients receiving polypharmacy were more likely to develop any DDI (9). In addition, some other factors could contribute to the high prevalence of potential DDIs found in our study. For instance, some authors have argued that patients treated in wards other than Infectious Diseases are at high risk for DDIs due to the unawareness of their treating physicians about clinically meaningful interactions (23). Another relevant factor for the high proportion of COVID-19 patients with potential DDIs was the presence of medical complications such as mechanical ventilation and sepsis that deserve further therapy usually in an Intensive Care Unit (ICU). In a similar research Brandariz-Nuñez and colleagues (21) identified ICU admission and number of prescribed drugs as risk factors for DDIs. In contrast with previous findings, we did not find any association between other variables such as age or comorbidities and any potential DDI.

A limitation of our study is the lack of clinical data to determine the clinical consequences of each potential DDI.

Besides, the cross-sectional design and the small number of patients receiving the studied therapies limit the external validity and inferences from our findings.

In conclusion, our analysis reveals a high proportion of patients treated with polypharmacy and at risk for clinical meaningful DDIs when using hydroxychloroquine and lopinavir/ritonavir for severe COVID-19.

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