

POTENTIAL DRUG-DRUG INTERACTIONS IN PATIENTS WITH COVID-19 IN A PUBLIC HOSPITAL IN BRAZIL

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Highlights: (1) 79.7% of Covid-19 patients had potential drug-drug interactions (pDDIs). (2) Anti-infectives, cardiovascular drugs, and anticoagulants were most involved in pDDIs. (3) Age 60-79 years, hypertension, ICU admission, and polypharmacy increased pDDIs risk. (4) Azithromycin + hydroxychloroquine increased the risk of ventricular arrhythmia. (5) Using ≤ 3 medications and shorter hospital stays were protective against pDDIs.

PRE-PROOF

(as accepted)

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ABSTRACT

Objective: To analyze the potential drug-drug interactions (pDDIs) of Covid-19 patients in a Brazilian public hospital. **Methods:** Cross-sectional, retrospective, descriptive, and analytical study conducted through the evaluation of medical records between March and November 2020. Drugs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system. The pDDIs were verified using the "drugs.com" database. **Results:** 79.7% of patients had pDDIs, totaling 483 possible interactions involving 113 different drugs. Among the pDDIs, 10.5% were classified as severe, 66.5% as moderate, and 23.0% as mild. The most common pDDIs involved anti-infective and cardiovascular drugs. Several factors were correlated with a higher occurrence of pDDI, such as being between 60 and 79 years old, hypertension, concurrent use of 4 to 7 drugs or more than 8 drugs, admission to the ICU, previous use of drugs for the cardiovascular system, prescription of anticoagulants, systemic hormonal preparations such as corticosteroids, and anti-infective agents for systemic use. On the other hand, being between 20 and 39 years old, using three or fewer drugs simultaneously, and staying less time hospitalized were associated with a decrease in the risk of pDDIs. **Conclusion:** Covid-19 patients have a high prevalence of pDDIs, demonstrating the need to identify and monitor their occurrence in public health institutions in order to increase patient safety.

Keywords: Pharmacoepidemiology; Risk factor; Drug interactions; Patient safety.

INTRODUCTION

Drug-drug interactions (DDIs) represent a significant concern in clinical practice. They occur when two or more drugs are administered and result in unexpected effects with their isolated use¹. Several factors can influence the occurrence of DDIs, such as the patient's age, health status, dose and duration of pharmacological therapy, in addition to genetics and lifestyle^{1,2}. DDIs can be classified into different types depending on the mechanism involved. Pharmacokinetic interactions involve changes in the absorption, distribution, metabolism or elimination of a drug due to the administration of another drug^{1,2}. In contrast, pharmacodynamic interactions alter the action of a drug in the body, regardless of its plasma concentration².

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However, some DDIs are unavoidable and may represent the only therapeutic option available, particularly in clinical scenarios where there is a shortage of alternatives, such as in patients with Covid-19. The complexity of Covid-19 treatment, which is often associated with comorbidities, can require the use of drug combinations potentially interactive, but essential for the adequate management of the clinical condition^{3,4}. In these cases, critical and careful evaluation by the healthcare professional becomes essential, ensuring the minimization of risks and the optimization of therapeutic results, through strict monitoring and individualized adjustment of therapies⁴.

In this sense, unmonitored DDIs can have serious consequences for patients, such as an increase or decrease in the therapeutic effect, toxicity, adverse effects, allergic reactions, among others⁵. Furthermore, DDIs are associated with a significant increase in health costs and the use of medical resources; thus, monitoring the drug chain is essential to ensure patient safety and reduce the risk of DDIs. This ranges from the correct prescription, dispensing and proper administration of the medication to monitoring the clinical response and early identification of DDIs⁶. However, not all DDIs are clinically relevant. Therefore, interactions between two or more drugs that may result in a clinically significant consequence for the patient are called potential drug-drug interactions (pDDIs) and are one of the preventable causes of adverse effects¹.

Therefore, it is extremely important to understand the prevalence and systematics involved in the occurrence of DDIs. Understanding the risks and how to avoid them directly impacts both the quality and safety of care provided to the patient and the costs for the health system⁵. Thus, the aim of this study is to identify pDDIs in patients diagnosed with Covid-19 in a public hospital in Brazil.

METHODS

Study participants, inclusion and exclusion criteria

This is a cross-sectional, retrospective, descriptive, and analytical study focusing on pDDIs found in patients diagnosed with Covid-19 from March to November 2020. The research was conducted at Hospital São Vicente de Paulo (HSVP), located in the municipality of

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Guarapuava, Paraná, Brazil. HSVP is a philanthropic healthcare institution founded in 1913. Due to its philanthropic nature, HSVP provides care through the Unified Health System (SUS) with a minimum percentage of 60%, although this percentage is often higher than 80%. HSVP performs medium-complexity procedures and is qualified for high complexity in the specialties of Cardiology, Neurology/Neurosurgery, High-Risk Pregnancy, and Oncology. In total, HSVP has 184 ward beds and 20 Intensive Care Unit (ICU) beds. Also, HSVP is a reference healthcare center for the 20 municipalities of the 5th Health Region of Paraná, covering a population of over 500 thousand inhabitants.

The study included patients aged 18 years or over who sought care at the emergency room with symptoms compatible with Covid-19, as well as patients hospitalized in the wards and ICU who received a positive diagnosis for the disease. A positive diagnosis for Covid-19 was confirmed by obtaining a positive result in at least one of the following tests: the real-time reverse transcription polymerase chain reaction test (rRT-PCR) or the rapid test. All selected patients had the clinical and pharmacological data required for the research recorded in their electronic medical records. The study was approved by the ethics and research committee of the HSVP, receiving approval number 03/2020, and by the ethics committee in research with human beings of the Universidade Estadual do Centro-Oeste, receiving CAAE nº 28847719.0.0000.0106 and Embodied Opinion nº 4.075.836.

Data Source

For the evaluation of clinical and pharmacotherapeutic variables, data were collected from electronic medical records of patients through remote and online access to the Hospital Management System – SGH®/SPDATA.

Drugs were classified according to the Anatomical Therapeutic Chemical Classification System (ATC) online version 2022⁶. The ATC classifies drugs based on their therapeutic properties, chemical structures, and organs or human body systems on which they act. In the present study, the second level of this classification was used, in which drugs are grouped into broad therapeutic classes, namely: A - Alimentary tract and metabolism; B - Blood and hematopoietic organs; C - Cardiovascular system; D - Dermatological; G - Genitourinary system and sexual hormones; H - Systemic hormonal preparations, excluding sex hormones and insulin; J - Anti-infectives for systemic use; L - Antineoplastic agents and

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immunomodulators; M - Musculoskeletal system; N - Nervous system; P - Antiparasitics, insecticides and repellents; R - Respiratory system; S - Sense organs; V - Various.

The pDDIs were verified with the drugs.com database, being classified according to the probability and intensity of effect in minor, moderate and major⁷. The drugs.com database was selected due to its accessibility, comprehensive coverage of drug combinations, and frequent updates; however, it is acknowledged that it is not considered a gold-standard reference in clinical research. The severity categories (minor, moderate, major) in drugs.com are defined based on the likelihood of clinical significance and the potential magnitude of effect: minor interactions have limited clinical relevance and generally require no intervention; moderate interactions may require monitoring or dose adjustment; and major interactions carry a significant risk of severe adverse effects and may require avoidance of the combination⁷.

Statistical analysis

Descriptive data were organized in Excel 2007 spreadsheets, subsequently analyzed and expressed in frequencies and percentage values. The chi-square test (χ^2) was used to assess the association between variables. The results obtained are expressed as the odds ratio (OR) accompanied by the lower and upper values of the 95% confidence interval (95% CI). The Haldane-Anscombe correction was used to calculate the OR when one of the cells had a zero value⁸. Probability values lower than 0.05 ($p < 0.05$) were considered statistically significant. All statistical analysis was performed using the Jamovi software (version 1.6).

RESULTS

Participant Characteristics

The study included 84 patients of both genders, who attended the hospital care service from March to November 2020 and who tested positive for SARS-CoV-2 by rRT-PCR or rapid test. The mean age was 57 ± 15.6 years, with a median of 56.5 years, a minimum age of 25 years and a maximum age of 94 years. It was identified that 37 patients (44.0%) were female and 47 (56.0%) were male. In addition, a total of 70 (83.3%) patients were discharged and 14 (16.7%) died during the analyzed period. The most frequent comorbidity was hypertension ($n=40/47.6\%$), followed by diabetes mellitus ($n=18/21.4\%$) and obesity ($n=17/20.2\%$).

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Medication use before and after hospital admission

As for the number of drugs used, the average was 2.0 ± 2.7 drugs per patient before hospital admission. After hospital admission, the mean number of medications increased to 4.6 ± 2.7 drugs per patient. Thus, the total administration of medications totaled 6.3 ± 4.1 medications/patient, with a minimum of 1 ($n=4/3.4\%$) and a maximum of 23 ($n=1/0.84\%$). The drugs most used by the 84 patients before admission were losartan ($n=21/25.0\%$), followed by metformin ($n=11/13.0\%$) and amlodipine ($n=7/8.3\%$). On the other hand, the most prescribed drugs in hospitals were azithromycin ($n=62/73.8\%$), heparin ($n=57/67.8\%$) and ceftriaxone ($n=46/54.7\%$). **Figure 1** shows data about the use of medications, grouped into pharmacological classes, according to the ATC.

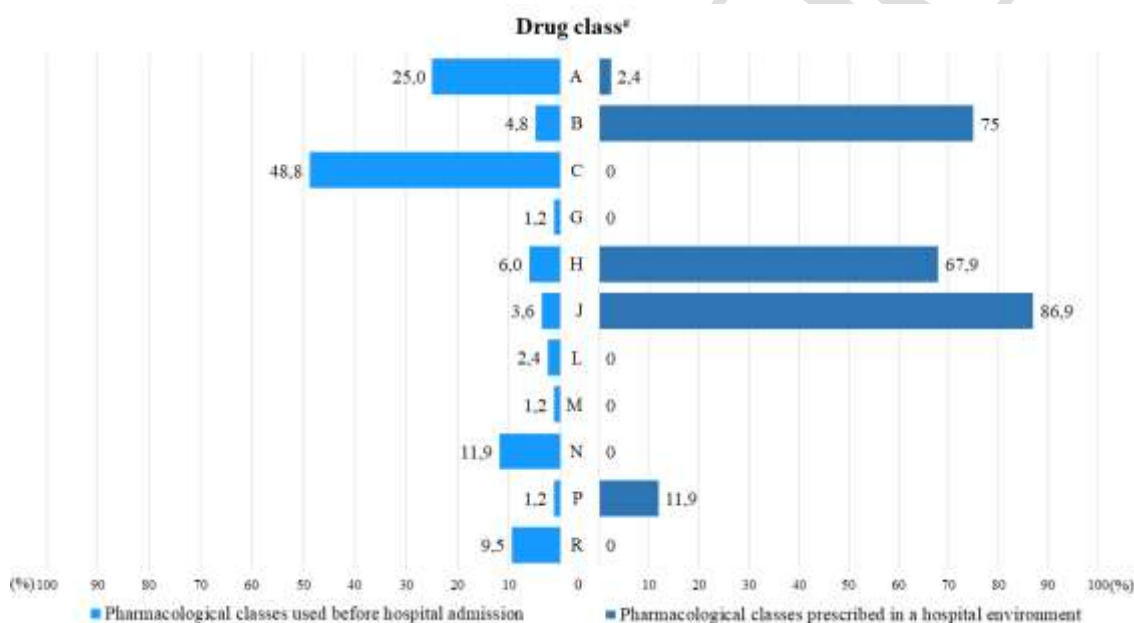


Figure 1. Percentage distribution of drug classes used by patients ($n=84$).

[#]According to ATC: A- Alimentary tract and metabolism; B- Blood and hematopoietic organs; C- Cardiovascular system; Genitourinary system and sex hormones; H- Systemic hormonal preparations, excluding sex hormones and insulins; J- Anti-infectives for systemic use; L- Antineoplastic and immunomodulatory agents; M- Musculoskeletal system; N- Nervous system; P- Antiparasitic, insecticide and repellent products; R- Respiratory system.

Source: Authors.

Distribution of pDDIs

A total of 483 pDDIs were detected in the pharmacotherapy of 67 patients (79.7%), related to 113 different medications, with the occurrence of 311 different interactions. The average number of interactions per patient was 5.75 ± 9.3 , so that 50 individuals (42.0%) had

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more than one interaction, with a minimum number of interactions of 1 (n=17/14, 3%) and the maximum 55 (n=1/0.8%). According to the ATC, most drugs involved in the detected pDDIs were related to the classes of general anti-infectives for systemic use (J: n=132.5; 27.4%), acting on the cardiovascular system (C: n=110; 22.7%), blood and hematopoietic organs (B: n=67.5; 13.9%), systemic hormonal preparations, excluding sex hormones and insulins (H: n=58.5; 12.1%) and food and metabolism (A: n=37.5; 7.7%). About 88% of the pDDIs recorded in the study were attributed to 10 drugs, which are shown in **Table 1**.

Table 1. Main drugs involved in pDDIs (n=483).

Drug	Number of pDDIs (n; %)
Heparin	94 (19.5)
Azithromycin	52 (10.8)
Hydrocortisone	50 (10.4)
Dexamethasone	49 (10.1)
Losartan	45 (9.3)
Ceftriaxone	40 (8.3)
Metformin	29 (6.0)
Furosemide	27 (5.6)
Spironolactone	23 (4.8)
Ciprofloxacin	19 (3.9)
Others	55 (11.3)

Source: Authors.

Distribution of pDDIs based on its severity

The study categorized drug interactions based on their severity. Analyzing the potential of pDDIs, it was observed that 51 (10.5%) were major, followed by 321 (66.5%) moderate and another 111 (23.0%) were minor. **Table 2** presents the 10 most frequent pDDIs found in the study, as well as their consequences.

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Table 2. pDDIs most frequently found in the study (n= 483).

Drugs	Frequency (n; %)	Consequence of drug interaction	Gravity
Ceftriaxone + heparin	34 (7.0)	Increased risk of bleeding	Minor
Heparin + losartan	17 (3.5)	Increased risk of hyperkalemia	Moderate
Dexamethasone + Losartan	9 (1.9)	Antagonism of the antihypertensive effect	Moderate
Azithromycin + hydroxychloroquine	8 (1.7)	Increased risk of ventricular arrhythmia	Major
Piperacillin + heparin	7 (1.4)	Increased risk of bleeding	Minor
Hydrocortisone + Losartan	6 (1.2)	Antagonism of the antihypertensive effect	Moderate
Piperacillin + Azithromycin	6 (1.2)	Antagonism of the effect of piperacillin	Minor
Dexamethasone + amlodipine	5 (1.0)	Antagonism of the antihypertensive effect	Moderate
hydrocortisone + metformin	5 (1.0)	Decreased antidiabetic effect	Moderate
Amikacin + polymyxin B	4 (0.8)	Increased risk of neurotoxicity and nephrotoxicity.	Major

Source: Authors.

Factors associated with the development of pDDIs

After applying the chi-square test, the results indicated that several factors were significantly associated with an increased risk of developing pDDIs. Among the factors, the following stand out: being between 60 and 79 years old (OR: 10.1, 95% CI: 1.27 - 81.15, $p = 0.009$); having hypertension (OR: 22.3, 95% CI: 2.79 - 178, $p < 0.001$); concomitant use of 4 to 7 drugs (OR: 4.53, 95% CI: 1.33 - 15.4, $p = 0.011$) or more than 8 drugs (OR: 22.3, 95% CI: 1.29 - 388, $p = 0.002$); ICU admission (OR: 5.38, 95% CI: 1.14 - 25.45, $p = 0.021$); previous use of drugs for the cardiovascular system (class C) (OR: 23.7 95% CI: 2.97 - 189, $p < 0.001$); prescription of anticoagulants (class B) (OR:40; 95% CI: 9.18 - 174, $p < 0.001$), systemic hormonal preparations such as corticosteroids (class H) (OR:4.20; 95% CI: 1.38 -12.8, $p = 0.008$) and anti-infectives for systemic use (class J) (OR: 6.76; 95% CI: 1.76-26.1, $p = 0.002$). Furthermore, the use of 0 to 3 drugs concomitantly (OR: 0.009; 95% CI: 0.002 - 0.06, $p < 0.001$) showed a strong protective association, indicating that the lower the number of drugs used, the lower the risk to develop pDDIs.

Furthermore, the following factors were not statistically significant (95% CI included 1), though they may warrant further investigation in larger samples: being between 20-39 years old (OR: 0.28; 95% CI: 0.07 - 1.03, $p = 0.046$), using a smaller number of medication (OR: 0.009; 95% CI: 0.002-0.1, $p < 0.001$) or hospital stay from 1 to 7 days (OR: 0.06; 95% CI: 0.003 - 1.01, $p = 0.006$). On the other hand, having diabetes mellitus (OR: 13.1; 95% CI: 0.75

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- 229.0, $p = 0.016$), being hospitalized between 8 and 14 days (OR: 8.67; 95% CI: 0.49 - 153, $p = 0.048$) and previous use of drugs for the alimentary tract and metabolism (class A) (OR: 16.2; 95% CI: 0.93 - 28, $p < 0.008$) were not statistically significant factors (95% CI included the value 1). These results should be interpreted with caution, as the absence of statistical significance may reflect sample size limitations rather than a true lack of association. More details about the epidemiological data and risk factors associated with the development of pDDIs are presented in **Table 3**.

Table 3. Risk factors associated with the development of pDDIs among study participants (n=84).

Variable	Parameters	Frequency (%)	pDDIs		p value	OR (95% IC)
			Yes	No		
Sex						
	Male	47 (56,0)	38	9	0,779	0,86 (0,29-2,50)
	Female	37 (44,0)	29	8		
Age distribution (in Years)						
	20-39	12 (14,3)	7	5	0,046*	0,28 (0,07-1,03)
	40-59	38 (45,2)	28	10	0,208	0,50 (0,17-1,48)
	60-79	27 (32,1)	26	1	0,009*	10,1 (1,27-81,15)
	>80	7 (8,3)	6	1	0,682	1,57 (0,18-14,02)
Comorbidities						
	Hypertension	40 (47,6)	39	1	<0,001*	22,3 (2,79-178)
	Cardiac insufficiency	7 (8,3)	7	0	0,164 [#]	4,34 (0,23-79,8)
	Asthma	6 (7,1)	6	0	0,200 [#]	3,70 (0,19-68,9)
	COPD	5 (6,0)	5	0	0,245 [#]	3,08 (0,16-58,4)
	Obesity	17 (20,2)	16	1	0,099	5,02 (0,61-40,9)
	Diabetes melitus	18 (21,4)	18	0	0,016 ^{*#}	13,1 (0,75-229)
	Hypothyroidism	4 (4,8)	3	1	0,808	0,75 (0,07-7,70)
Amount of medication						
	0-3	15 (17,9)	2	13	<0,001*	0,009 (0,002-0,06)
	4-7	43 (51,2)	39	4	0,011*	4,53 (1,33-15,4)
	+8	26 (31,0)	26	0	0,002 ^{*#}	22,3 (1,29-388)
Admission to the ICU						
	Yes	30 (35,7)	28	2	0,021*	5,38 (1,14-25,45)
	No	54 (64,3)	39	15		
Hospitalization days						

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1-7	62 (73,8)	45	17	0,006* [#]	0,06 (0,003-1,01)
8-14	13 (15,5)	13	0	0,048* [#]	8,67 (0,49-153)
>15	9 (10,7)	9	0	0,110 [#]	5,68 (0,315-103)
Pharmacological classes used before hospital admission^{##}					
A	21 (25,0)	21	0	0,008* [#]	16,2 (0,93-28)
B	4 (4,8)	4	0	0,302 [#]	2,5 (0,13-48,3)
C	41 (48,8)	40	1	<0,001*	23,7 (2,97-189)
G	1 (1,2)	1	0	0,612 [#]	0,79 (0,03-20,2)
H	5 (6,0)	5	0	0,245 [#]	3,08 (0,16-58,4)
J	3 (3,6)	3	0	0,374 [#]	1,90 (0,09-38,5)
L	2 (2,4)	2	0	0,471 [#]	1,34 (0,06-29,1)
M	1 (1,2)	1	0	0,612 [#]	0,489 (0,03-20,2)
N	10 (11,9)	10	0	0,090 [#]	6,39 (0,35-115)
R	8 (9,5)	8	0	0,134 [#]	5 (0,27-91)
P	1 (1,2)	0	1	0,046 [#]	0,08 (0,003-2,09)
Pharmacological classes prescribed in a hospital environment^{##}					
A	2 (2,4)	2	0	0,471 [#]	1,34 (0,06-29,1)
B	63 (75,0)	60	3	<0,001*	40 (9,18-174)
H	57 (67,9)	50	7	0,008*	4,20 (1,38-12,8)
J	73 (86,9)	62	11	0,002*	6,76 (1,76-26,1)
P	10 (11,9)	10	0	0,090 [#]	6,39 (0,36-115)

OR: Odds ratio; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; ICU: Intensive Care Unit. *p < 0.05. [#]Haldane-Ascombe fix applied. ^{##} According to the ATC: A- Alimentary tract and metabolism; B- Blood and hematopoietic organs; C- Cardiovascular system; G- Genitourinary system and sex hormones; H- Systemic hormonal preparations, excluding sex hormones and insulins; J- Anti-infectives for systemic use; L- Antineoplastic agents and immunomodulators; M- Musculoskeletal system; N- Nervous system; P- Antiparasitic products, insecticides and repellents; R- Respiratory system.

Source: Authors.

DISCUSSION

Evaluating patients admitted to a Brazilian public hospital during the first wave of the Covid-19 pandemic, we found that almost 80% had pDDIs. Prevalence rates of pDDIs in patients with Covid-19 vary considerably in the literature: 68% in northern Italy, 87.4% in Spain and 37.9% in Iran⁹⁻¹¹.

During the first wave of the pandemic, there were no specific and effective treatments for Covid-19. Thus, several drugs were used empirically and without rationalization, increasing the risk of pDDIs^{10,11}. In fact, in our study, a single patient had 55 pDDIs, while in another

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study it was reported that the maximum number of pDDIs in a patient was 10, which may be associated with the greater variety of drugs used by the patients in our study¹².

Our results agree with the literature in the statement that the number of drugs used is related to the probability of occurrence of pDDIs, with a higher risk observed in cases of polypharmacy¹². Indeed, Cantudo-Cuenca and cols. (2021) demonstrated that the presence of clinically relevant pDDIs was associated with the number of comorbidities and medications prescribed during hospitalization, in such a way that for each additional medication prescribed there was a 1.42 times greater chance of occurrence of pDDIs¹¹. These findings suggest that the increase in health problems and the need for multiple treatments may lead to an increased risk of hospitalizations and a reduction in the patient's quality of life.

In different studies of patients with Covid-19, a wide variation was observed in the prevalence rates of pDDIs, as well as in the average number of drugs used. A study carried out in Turkey identified an average of 8 drugs per patient, ranging from 1 to 11, with a total of 605 pDDIs¹³. Another study found similar results, with an average of 8 medications per patient, ranging from 6 to 9, and a total of 904 pDDIs⁹. Both studies presented an average higher than that found in our research. However, another study reported that the mean number of medications was 5.6 ± 4.1 , a lower result than that found in our study¹⁰. In Brazil, studies prior to the Covid-19 pandemic also confirm this variability. In an ICU in the south of the country, it was observed that the average number of drugs prescribed was 10.0 ± 5.2 , and 91.4% of patients had at least one pDDI, with an average of 5.8 ± 6.1 pDDIs per patient, and a single patient had 40 drug interactions¹⁴.

In the evaluated Covid-19 patients, we identified a significant association between the presence of hypertension and pDDIs. This correlation is supported by previous studies^{9,15}. Also found that hypertension was the most common comorbidity in these patients and was related to a higher incidence of pDDIs. Therefore, in our study, we found that patients who were already using medication for the cardiovascular system before hospital admission had an approximately 23 times greater risk of developing a pDDI.

ICU admission is an aggravating factor in Covid-19. In this sense, a retrospective analysis of 254,288 hospitalizations of patients with a positive diagnosis for Covid-19 in Brazil, between February and August 2020, revealed that 6 out of 10 patients admitted to the ICU died¹⁶. In our study, patients admitted to the ICU were about 5 times more likely to have pDDIs.

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This finding is supported by previous studies, who demonstrated that a greater number of pDDIs is associated with a longer ICU stay^{17,18}.

In our study, the use of anticoagulants was associated with 40 times more chances of having a pDDI, with heparin being the main representative of this class, present in 19.5% of pDDIs. The most frequent pDDI occurred between ceftriaxone and heparin. Although this pDDI was considered minor, heparin use must be monitored due to increased risk of hemorrhage. The high use of this drug class in patients with Covid-19 is justified by the coagulopathy generated by SARS-CoV-2, which is one of the main factors related to mortality from the infection¹⁹.

Nevertheless, a significant correlation was observed between the prescription of corticosteroids and antibiotics and the occurrence of pDDIs. Users of these drugs were 4.20 and 6.76 times more likely to develop pDDI, respectively. Antibiotics are commonly used for prophylaxis and treatment of secondary bacterial infections to viral infections, while corticosteroids are used to control the cytokine storm caused by SARS-CoV-2 infection²⁰. A study conducted in Italy showed that among patients treated with corticosteroids, approximately 73% had pDDIs with concomitant therapies²¹.

Besides the risk of bacterial infections in patients with viral infections, the frequent prescription of antibiotics in patients with Covid-19 also is due to the similarity of symptoms between bacterial pneumonia and viral infections²². Azithromycin was the most commonly used antibiotic in our study, representing 10.8% of all pDDIs. In our study, the combination of azithromycin and hydroxychloroquine was found to result in the most prevalent major pIDD (n=8). This finding is consistent with other studies that have also frequently reported this interaction^{10,13}. However, it has already been shown that this combination, whether accidental or intentional, does not improve survival or length of stay in patients with Covid-19²³. Rather, it may increase the risk of serious cardiovascular adverse events, QTc interval prolongation, and ventricular arrhythmia²⁴.

It is crucial to consider that the pharmacological classes related to pDDIs observed in our study, such as anticoagulants, corticosteroids, and anti-infectives for systemic use, are often indispensable in the management of Covid-19, especially in severe cases. Although DDIs are almost inevitable, their clinical relevance should be carefully assessed^{10,11}. Herein, we suggest that, although many of these pDDIs are of moderate severity, their occurrence may potentially

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be associated with adverse clinical outcomes, including prolonged hospital stay and increased mortality risk, as observed in patients with a higher number of pDDIs in this and other studies. Therefore, the management of pDDIs should not be neglected, even in the face of limitations in therapeutic alternatives.

In our study, we found a low prevalence of major pDDIs ($n=51/10.5\%$), in contrast to other studies that reported a high prevalence of them^{9, 10,13}. Furthermore, in our study, we observed that most pDDIs were related to the class of general anti-infectives for systemic use. In contrast, a study identified that drugs that act on the alimentary tract and metabolism had the highest number of pDDIs with drugs for Covid-19 ($n=11/18.3\%$)²⁵. In addition, another study pointed out that most pDDIs were related to cardiovascular system medications ($n = 252/45.6\%$)¹¹.

It is important to mention that the study was carried out at the beginning of the pandemic, representing a scenario that may change now, with the availability of more therapeutic options and greater knowledge about the pathogenesis of COVID-19. Furthermore, the generalizability of the results may be restricted due to the specific nature of the sample, which included patients treated at a public hospital in the interior of Brazil. In this context, it is crucial to consider that the people treated at this hospital may have limited resources for the adequate treatment of their morbidities. Therefore, results may not be representative of other hospitals. Another limitation concerns the precision and completeness of the detection of pDDIs, which depend on the quality and updating of the databases used, as well as the availability and accuracy of the information recorded in the medical records. In addition, the use of a single database represents a methodological limitation, as the sensitivity and specificity of pDDI detection may vary compared to using multiple databases, such as LexiComp or Micromedex. These limitations must be considered when interpreting the results and highlight the need for additional studies to complement and corroborate the findings made. Additionally, the statistical analysis was restricted to bivariate methods (chi-square and odds ratio), without a multivariate logistic regression model. This limits the ability to control confounding variables, such as age, number of comorbidities, and polypharmacy are interrelated. Future studies should consider multivariable approaches to better isolate independent predictors of pDDIs.

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CONCLUSION

Herein, we reported for the first time the pDDIs in patients diagnosed with Covid-19 in a Brazilian public hospital. The results revealed a high incidence of pDDIs, with 79.7% of patients presenting at least one DDI, reflecting the complexity of pharmacological treatment in patients with multiple comorbidities and using polypharmacy. Among the interactions observed, the most involved pharmacological classes were anti-infectives for systemic use, drugs that act on the cardiovascular system, and agents that affect the blood and hematopoietic organs. Factors such as advanced age, presence of hypertension, use of a high number of drugs, admission to the ICU, and use of specific pharmacological classes (anticoagulants, corticosteroids and anti-infectives) were significantly associated with an increased risk of pDDIs. In contrast, a reduced number of drugs used and shorter hospitalizations were found as protective factors against the development of pDDIs.

Of note, this study demonstrates the consequences of empirical and non-rationalized use of drugs during the Covid-19 pandemic, evidenced by the high number of different drugs involved, which contributed to a higher incidence of pDDIs. These findings highlight the urgent need to identify and monitor pDDIs within the public hospital environment to prevent preventable adverse events, mitigate hospitalization costs, and prioritize patient safety. Moreover, it is recommended to implement alert systems for pDDIs and review drug policies during emergencies to ensure more rational drug use. Considering the complexity of Covid-19 treatment and the associated comorbidities, rationalizing drug use is essential to ensure optimized care and minimize the risks associated with pDDIs. In this context, the clinical pharmacist plays a central role in the identification, prevention, and management of pDDIs. Practical interventions such as medication reconciliation at hospital admission and discharge, the use of clinical decision support systems with pDDI alerts, and antimicrobial stewardship programs are strongly recommended as strategies to reduce the burden of drug interactions in hospitalized patients with complex pharmacotherapy profiles.

REFERENCES

1. Fitzmaurice MG, Wong A, Akerberg H, et al. Evaluation of potential drug-drug interactions in adults in the intensive care unit: a systematic review and meta-analysis. *Drug Saf.* 2019;42(9):1035-1044.

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IN A PUBLIC HOSPITAL IN BRAZIL**

2. Niu J, Straubinger RM, Mager DE. Pharmacodynamic drug-drug interactions. *Clin Pharmacol Ther.* 2019;105(6):1395-1406.
3. O'Hare AM, Vig EK, Iwashyna TJ, et al. Complexity and challenges of the clinical diagnosis and management of long COVID. *JAMA Netw Open.* 2022;5(11):e2240332.
4. Sousa APR, Melo TS, Linhares MI, Mormino KBNT. Impacto das interações medicamentosas em ambiente hospitalar e papel do farmacêutico clínico nesse cenário: revisão sistemática de literatura. *Saúde (Santa Maria).* 2023;49(2).
5. Rasool MF, ur Rehman A, Khan I, et al. Assessment of risk factors associated with potential drug-drug interactions among patients suffering from chronic disorders. *PLoS One.* 2023;18(1):e0276277.
6. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index [Internet]. Oslo: WHOCC; [cited 2023 Apr 18]. Available from: https://www.whocc.no/atc_ddd_index/
7. Drugs.com. Drug interactions checker [Internet]. [cited 2023 Apr 18]. Available from: https://www.drugs.com/drug_interactions.html
8. Weber F, Knapp G, Ickstadt K, Kundt G, Glass Ä. Zero-cell corrections in random-effects meta-analyses. *Res Synth Methods.* 2020;11(6):913-919.
9. Mahboobipour AA, Baniasadi S. Clinically important drug-drug interactions in patients admitted to hospital with COVID-19: drug pairs, risk factors, and management. *Drug Metab Pers Ther.* 2020;36(1):9-16.
10. Cattaneo D, Pasina L, Maggioni AP, et al. Drug-drug interactions and prescription appropriateness in patients with COVID-19: a retrospective analysis from a reference hospital in Northern Italy. *Drugs Aging.* 2020;37(12):925-933.
11. Cantudo-Cuenca MD, Gutiérrez-Pizarra A, Pinilla-Fernández A, 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(1):12414.
12. Benetti JL, Benetti C, Rodrigues AF, et al. Potential drug interactions in patients' prescriptions in the infectious disease unit of a university hospital. *Braz J Health Rev.* 2021;4(3):11118-11133.
13. Kilit TP, Özyiğit F, Erarslan S, Onbaşı K. Evaluation of potential drug-drug interactions and polypharmacy in hospitalized COVID-19 patients. *Afr Health Sci.* 2022;22(4):597-606.
14. Casanova O, Tavares da S, Penteado S, Linartevichi VF. Análise de interações medicamentosas em unidade de terapia intensiva em um hospital no sul do Brasil. *FAG J Health.* 2019;1(1):81-88.

**POTENTIAL DRUG-DRUG INTERACTIONS IN PATIENTS WITH COVID-19
IN A PUBLIC HOSPITAL IN BRAZIL**

15. Santos KFS, Silva CML, Barros IMC, Silva LM. Potenciais interações medicamentosas em pacientes idosos da clínica médica de um hospital universitário. *Scientia Plena*. 2022;18(6):064501.
16. Ranzani OT, Bastos LSL, Gelli JGM, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. *Lancet Respir Med*. 2021;9(4):407-418.
17. Reis AMM, Cassiani SHB. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. *Clinics (Sao Paulo)*. 2011;66(1):9-15.
18. Moura C, Prado N, Acurcio F. Potential drug-drug interactions associated with prolonged stays in the intensive care unit: a retrospective cohort study. *Clin Drug Investig*. 2011;31(5):309-316.
19. Atallah B, Sadik ZG, Salem N, et al. The impact of protocol-based high-intensity pharmacological thromboprophylaxis on thrombotic events in critically ill COVID-19 patients. *Anaesthesia*. 2021;76(3):327-335.
20. Santana DM, Bueno FG, Silva LL. Prescrição de medicamentos potencialmente inapropriados para idosos em um hospital público. *J Assist Farmacocon*. 2017;2(1):20-30.
21. Cattaneo D, Pasina L, Conti F, et al. Risks of potential drug-drug interactions in COVID-19 patients treated with corticosteroids: a single-center experience. *J Endocrinol Invest*. 2021;44(12):2849-2851.
22. Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles! *Clin Microbiol Infect*. 2020;26(7):808-810.
23. Sivapalan P, Ulrik CS, Lapperre TS, et al. Azithromycin and hydroxychloroquine in hospitalised patients with confirmed COVID-19: a randomised double-blinded placebo-controlled trial. *Eur Respir J*. 2022;59(1):2100752.
24. Fiolet T, Guihur A, Rebeaud ME, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2021;27(1):19-27.
25. Jeong E, Nelson SD, Su Y, Malin B, Li L, Chen Y. Detecting drug-drug interactions between therapies for COVID-19 and concomitant medications through the FDA adverse event reporting system. *Front Pharmacol*. 2022;13:938552.

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