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Pharmacotherapeutic profile of patients admitted with COVID-19 at a university hospital

Perfil farmacoterapêutico de pacientes internados com COVID-19 em hospital universitário

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ABSTRACT
To describe pharmacotherapy in the home and hospital setting and the association with clinical-demographic characteristics of patients hospitalized with COVID-19. Observational, cross-sectional study with retrospective data collection. The variables of interest were medications for COVID-19, chronically used, and used during hospital admission. Non-parametric tests were used to compare and correlate the variables, and the statistical significance adopted was 5%. It was identified that 34.8% of patients used some medication for COVID-19 before hospitalization, and 71.6% (n=255) were undergoing chronic treatments. Azithromycin was the most used medication for COVID-19, and 28.1% of patients had polypharmacy. Days of hospitalization (p=<0.001) and intensive care (p=<0.001) had a strong correlation with the number of medications used. Higher education, impaired renal function, comorbidities, and polypharmacy were associated with the profile of previous users of medications for COVID-19. Intensive care and death were related to a higher number of medications used than other patients.

Keywords: Brazil. COVID-19. Drug Therapy. Hospitals. Pharmacoepidemiology.

RESUMO
Descrever a farmacoterapia no cenário domiciliar e hospitalar e a associação com características clínico-demográficas de pacientes hospitalizados com COVID-19. Estudo observacional, transversal e com coleta de dados retrospectiva. As variáveis de interesse foram medicamentos para COVID-19, de uso crônico e utilizados na internação hospitalar. Testes não-paramétricos compararam e correlacionaram as variáveis e a significância estatística adotada foi de 5%. Identificou-se que 34,8% dos pacientes administrou algum medicamento para COVID-19 antes da internação e 71,6% realizavam tratamentos crônicos. Azitromicina foi o medicamento mais utilizado para COVID-19 e 28,1% dos pacientes apresentavam polifarmácia. Dias de internação (p=<0,001) e de terapia intensiva (p=<0,001) teve forte correlação com número de medicamentos utilizados. Ensino superior, função renal comprometida, ter comorbidades e polifarmácia foram associados ao perfil de usuário prévio de medicamentos para COVID-19. Terapia intensiva e óbito foram relacionadas ao maior número de medicamentos utilizados que os demais pacientes.

Palavras-chave: Brasil.COVID-19. Tratamento Farmacológico. Hospitais. Farmacoepidemiologia.

INTRODUCTION

In 2019, the severe acute respiratory syndrome coronavirus (Sars-Cov-2) represented a major threat to global public health.[1] In the first two waves of COVID-19 in Brazil, the patients most affected by complications of the disease were older adults and those who had chronic diseases, which are generally related to the use of multiple medications.[2,3] Faced with the uncertainties of an unknown disease, medications without proven efficacy were being used to prevent, alleviate symptoms, or treat both in the outpatient and hospital settings.[4]

Problems related to the inappropriate and empirical use of medicines, polypharmacy, risks of supply chain disruption, and reduction in stocks of strategic inputs made COVID-19 worrying for health managers and professionals. [5–7] In Brazil, guidelines were published in 2021 for outpatient and hospital drug treatment of COVID-19, but in most hospitals, pharmacotherapy continued to be defined by each prescriber.[8,9]

In a country with large regional and cultural differences, variations in the use and prescription of drugs during the evolution of the pandemic are to be expected. [8] In Brazil, the most significant studies are limited to describing patients' clinical characteristics and outcomes, providing little data on the actual use of medications during the pandemic.[10,11] On the international scenario, studies have evaluated the discrepancies between drug prescription patterns for COVID-19 compared to local recommendations in force at the time.[12,13] Other authors discuss commonly used medications and the prevalence of self-medication during the pandemic.[14,15]

To date, no studies have been found that characterize the profile of patients who used medications for COVID-19, the impact of medication use on hospital outcomes, and likely changes in the prescription profile during the pandemic. Knowing the population's medication use profile and its implications makes it possible to develop strategies for prevention and health promotion, providing health services with subsidies to structure programs for the rational use of medications and offering adequate care to the population.

In this context, considering the limited number of real-life studies on the use of medicines during the COVID-19 in Brazil, the objective of this study was to describe pharmacotherapy in the home and hospital setting and check the association with the clinical-demographic characteristics of hospitalized patients with COVID-19 at a reference university hospital for severe cases in the state of Rio Grande do Sul (RS), Brazil.

METHODOLOGY

Analytical and cross-sectional study with retrospective data collection. Patients aged 18 years or over hospitalized between March 17, 2020 - the date of the first patient diagnosed with COVID-19 in the hospital - and September 15, 2021, were included. Only patients with a Polymerase Chain Reaction (PCR) test positive for Sars-Cov-2 were selected. The period from March to November 2020 was considered the first wave, and from that period onwards, it was considered the second wave.

Patients whose hospitalization lasted less than 48 hours, and/or the reason for hospitalization was not related to COVID-19, and/or whose health outcome was unknown due to evasion, transfer, or hospitalization that had not yet been finalized were not included. We decided to exclude patients who died in less than 24 hours and were hospitalized for less than 48 hours due to incomplete data for the variables of interest.

The research location is a public, general, high-complexity university hospital, which mainly serves patients from the Unified Health System (SUS). It is located in the capital

of the state of Rio Grande do Sul (RS), one of the reference centers for COVID-19 care, and has the highest number of intensive care beds in the state.[16] Both prescription and medication flow are computerized.

The variables of interest were sociodemographic data (sex, age, race, education, and geographic region of residence in RS), clinical history (comorbidities, body mass index [BMI] classification, estimated glomerular filtration rate classification [eGFR], smoking history, immunization for COVID-19, oxygenation upon admission), complications during hospitalization (need and days in intensive care bed, acute respiratory failure [ARF], pulmonary thromboembolism [TEP], deep vein thrombosis [DVT], delirium, ventilator-associated pneumonia [VAP] and need for dialysis) and medication history. Immunization against COVID-19 was only considered among those hospitalized as of January 18, 2021, which marked the beginning of vaccine distribution in the state. Polypharmacy was considered as the habitual use of five or more medications. The medicines were classified according to the Anatomical Therapeutic Chemical (ATC) adopted by the WHO Collaborating Center for Drugs Statistics Methodology.

Demographic and clinical characteristics were obtained through the institution's database[17], and information that cannot be extracted through computerized reports was actively collected from medical records. Data on previously used medications were extracted from information self-reported by the patient and/or family members, and medications used during hospitalization were obtained from reports of dispensed medications.

To control potential bias and confounding factors, cases were ordered by date of admission, and random sampling was performed in blocks. Information bias was minimized by excluding records with more than 5% incompleteness. Memory bias, state of consciousness upon admission, and limitations of the computerized system may have underestimated some variables.

Among the patients with COVID-19 (n=7,052) received in the hospital, 6,719 required hospitalization. From the list of 4,224 patients who met the inclusion criteria, the sample size was estimated considering the calculation for prevalence studies using the WINPEPI® software. A maximum absolute error of 0.05, a variability of 0.5, and a confidence interval of 95% were adopted, requiring a sample of at least 356 medical records.

Descriptive data were collected on a specific form, entered into a Microsoft Excel spreadsheet, and subjected to statistical analysis. Categorical variables were described as proportions and continuous variables as median ± interquartile range. The normal distribution of quantitative data was assessed using the Shapiro-Wilks test. Categorical variables were compared using Fisher's exact test, Pearson's Chi-Square, or Yates' continuity correction test. Continuous variables were compared using the Mann-Whitney test, and the correlation between variables was analyzed using the Spearman coefficient. The level of statistical significance considered was 5% ($p \leq 0.050$). All analyses were performed using SPSS 18.0.

The research was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre under opinion 4.672.349 and CAAE 44718021.3.0000.5327. The researchers declared that they knew and complied with the requirements of the General Data Protection Law (Law 13.709, of August 14, 2018) and signed the Data Use Commitment Term for the use of the COVID-19 Biobank, guaranteeing confidentiality, secrecy, and privacy of patients and professionals. They also declared that there was no conflict of interest that could interfere with the impartiality of the research.

This article follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies.[18]

RESULTS

We analyzed 356 medical records, of which, 56.5% (n=201) referred to male patients and a median age of 62.0 (IQR 47.0-72.0) years. The majority (n=165; 46.3%) of patients followed the therapeutic itinerary between emergency service, intensive care, and outpatient bed until the respective outcome (Figure 1). The most prevalent comorbidities were hypertensive (54.8%), endocrine (39.3%), circulatory (16.6%), respiratory (15.2%), genitourinary (14.3%) and mental (12.1%). Polypharmacy was present in 28.1% (n=100) of patients. A median of two (IQR 1.0 – 3.0) medications for COVID-19 symptoms were used before hospitalization and, upon hospital admission, a median of 15.5 (IQR 8.0-33.7) medications were dispensed per patient.

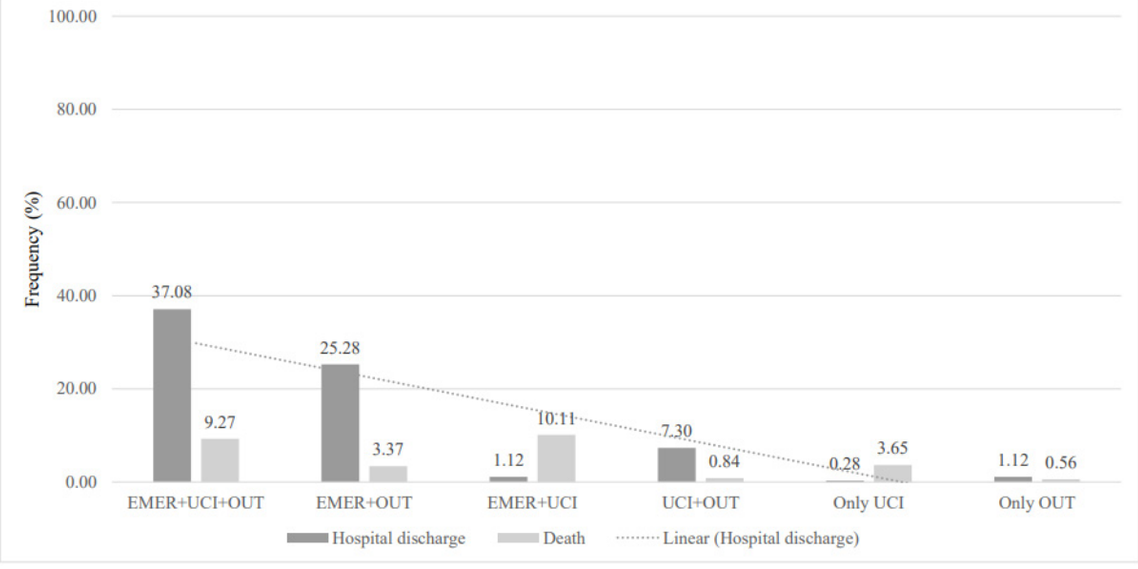

Figure 1. Outcome of patients hospitalized for COVID-19 for more than 48 hours according to the therapeutic itinerary between care units expressed as a percentage (n=356) (%). Legend: EMER: emergency service; ICU: intensive care unit; OUT: outpatient bed.

PREVIOUS USE OF MEDICATION FOR COVID-19

This study identified 124 (34.8%) patients who used some medication to prevent COVID-19 symptoms. The variables associated with previous use of medications for COVID-19 were higher education (p=0.004), moderate-severe renal function and renal failure upon admission (p=0.003), having two or more comorbidities (p=<0.001), and being polymedicated (p=0.002) (Table 1 and 2). No associations were detected between medication use and existing comorbidities.

Thirty drugs were used for symptoms and/or prevention of COVID-19 before hospitalization. The main anatomical groups, according to the ATC classification, were anti-infectives for systemic use (57.4%), systemic hormonal preparations (17.0%), and antiparasitics (11.1%). Among anti-infectives, antimicrobials for systemic use were the most used (95.7%), in which macrolides were the pharmacological subgroup with the highest frequency of use (85.0%), followed by beta-lactam antimicrobials associated with penicillin (26.5%). Simple corticosteroids were the systemic hormonal preparations used (100.0%). Antiparasitics were distributed into two therapeutic subgroups, anthelmintics (62.5%) and antiprotozoals (37.5%), highlighting the use of ivermectin and aminoquinolines. Azithromycin (67.7%), amoxicillin combined with clavulanate potassium (27.4%), prednisone (21.7%), ivermectin (15.3%), and dexamethasone (15.3%) were the most used medications.

Table 1. Sociodemographic characteristics of patients hospitalized with COVID-19 compared regarding the use of COVID medications prior to hospitalization and the use of chronic medications (n=356)

		Used COVID medication (n=124)			Used chronic medication (n=255)		
		n	%	p	n	%	p
Sex[a]	Male (n=201)	74	59.7	0.434	134	52.5	0.025*
	Female (n=155)	50	40.3		121	47.5[1]	
Age[a]	Less than or equal to 65 years old (n=215)	82	66.1	0.133	148	58	0.186
	Over 65 years old (n=141)	42	33.9		107	42	
Race[a]	Caucasian (n=294)	104	83.9	0.748	216	84.7	0.128
	Other races (black, brown, indigenous and yellow)	20	16.1		39	15.3	
Education[b]	Basic education (n=174)	48	38.7	0.004*	127	49.8	0.792
	High school (n=102)	42	33.9		73	28.6	
	University education (n=40)	22[1]	17.7		29	11.4	
	Unknown (n=40)	12	9.7		26	10.2	
Hospital outcome[a]	Hospital discharge (n=257)	92	74.2	0.622	185	72.5	0.914
	Death (n=99)	32	25.8		70	27.5	
Pandemic period[a]	First wave (n=143)	44	35.5	0.228	99	38.8	0.482
	Second wave (n=213)	80	64.5		156	61.2	
Institutionalized[a]	Yes (n=6)	2	1.6	1.000	4	1.6	1.000
	No (n=350)	122	98.4		251	98.4	

Legend: *Statistical significance considered at $p \leq 0.050$. [1] Significant differences ($p \leq 0.050$) between variables. [a]Yates continuity correction test; [b]Pearson's Chi-square test..

CHRONIC USE OF MEDICATIONS

Among patients, 255 (71.6%) were chronic medication users and 179 medications were reported. Among the main anatomical groups, the cardiovascular system stood out, with 40.8%, and the alimentary tract and metabolism (18.4%). The most commonly used medications were losartan (23.9%), metformin (22.7%), simvastatin (22.7%), omeprazole (21.9%), and amlodipine (21.1%).

History of use was more prevalent among male patients (n=134; 52.5%, p<0.025), with mild to mild-moderate renal function at admission (n=114; 45.2%, p=0.048), without oxygen supplementation (n=168; 65.9%, p<0.001), did not yet have a diagnosis of COVID-19 (n=134; 52.5%; p=0.006), two or more comorbidities (n =196; 76.9%; p<0.001), polymedicated (n=99; 38.8%; p<0.001) and need for intensive therapy (n=170; 66.7%; p=0.004) (Table 2).

Table 2. Clinical characteristics of patients hospitalized with COVID-19 compared regarding the use of medications for COVID prior to hospitalization and use of chronic medications (n=356)

		Used COVID medication (n=124)			Used chronic medication (n=255)		
		n	%	p	n	%	p
Smoking history (n=356) [a]	Active or ex	31	25.0	0.890	65	25.5	0.915
	No	93	75.0		190	74.5	
Body mass index [BMI] classification (n=310)[b]	Eutrophic	23	20.4	0.064	50	22.7	0.138
	Overweight	24	21.2		60	27.3	
	Obese	60	53.1		93	42.3	
	Malnourished	6	5.3		17	7.7	
Estimated glomerular filtration rate classification [eGFR] (n=353)[b]	Normal	45	36.6	0.003*	67	26.6[2]	0.048*
	Discreet to discreet-moderate	59	48.0		114	45.2	
	Moderate severe kidney failure	19	15.4[1]		71	28.2	
Oxygenation upon admission (n=355)[b]	Without oxygen supplementation	72	58.1	0.585	168	65.9[1]	<0.001*
	Oxygen therapy, non-invasive ventilation, high-flow nasal cannula and tracheostomy	38	30.6		67	26.3	
	Mechanical ventilation	14	11.3		20	7.8[2]	
Immunization for COVID-19 (n=174)[a]	Yes	10	14.9	1.000	21	16.7	0.426
	No	57	85.1		105	83.3	
Presence of comorbidities (n=356)[b]	None	31	25.0	<0.001*	7	2.7	<0.001*
	One comorbidity	33	26.6		52	20.4	
	Two or more comorbidities	60	48.4[1]		196	76.9[1]	
Polypharmacy (n=356)[a]	Yes	22	17.7[1]	0.002*	99	38.8	<0.001*
	No	12	82.3		156	61.2	
Days in intensive care bed (n=356)[b]	None	38	30.6	0.444	85	33.3	0.004*
	1 to 7 days	30	24.2		78	30.6	
	8 or more days	56	45.2		92	36.1	
Ventilator-associated pneumonia [VAP] (n=355)[a]	Yes	28	22.6	0.796	49	19.2	0.143
	No	96	77.4		206	80.8	
Pulmonary thromboembolism [TEP] (n=355)[a]	Yes	25	20.2	0.164	39	15.3	0.643
	No	99	79.8		216	84.7	
Deep vein thrombosis [DVT] (n=355)[a]	Yes	7	5.6	0.914	9	3.5	0.065
	No	117	94.4		246	96.5	
Acute respiratory failure [ARF] (n=355)[a]	Yes	29	23.4	0.132	69	27.1	0.326
	No	95	76.6		186	72.9	
Delirium (n=355)[a]	Yes	5	4.0	0.313	15	5.9	0.882
	No	119	96.0		240	94.1	
Dialysis (n=355)[a]	Yes	20	16.1	0.311	48	18.8	0.751
	No	104	83.9		207	81.2	

Legend: *Statistical significance considered at $p \leq 0.050$. [1] Significant differences ($p \leq 0.050$) between variables. [a]Yates continuity correction test; [b]Pearson's Chi-square test..

MEDICATION USE DURING HOSPITALIZATION

We observed that 244 drugs were dispensed during hospital admission. Patients who required intensive therapy used a median of 26 drugs (75% IQR 13.0-37.0; p<0.001), and patients who remained in a hospital bed used 8 drugs (75% IQR 6.0-12.0). Patients who died used more medications compared to those who were discharged (13.0; 75% IQR 7.0-26.0 versus 32.0; 75% IQR 18.0-41.25; p<0.001). The number of medications used showed a strong positive correlation with the days of hospitalization (ρ=0.800; p=<0.001) and intensive care (ρ=0.715; p=<0.001) and a weak positive correlation with the number of comorbidities (ρ= 0.219; p=<0.001).

The most frequently dispensed medications were dipyrone (n=323, 90.7%), dexamethasone (n=272; 76.4%), enoxaparin (n=269; 75.5%), omeprazole (n=226; 63.4%), and paracetamol (n=188; 52.8%). We identified 437 drug presentations. Regarding the pharmaceutical form, 38.9% (n=170) corresponded to tablets or capsules, 35.4% (n=155) to injectables, and 16.02% (n=70) to drops, solution, powder, or oral suspension. In intensive care, the most dispensed medications were dipyrone (n=216; 87.4%), omeprazole (n=193; 78.2%), dexamethasone (n=182; 73.7%), enoxaparin (n=165; 66.8%), fentanyl (n=162; 65.7%), and midazolam (n=162; 65.7%). The injectable pharmaceutical form was the most dispensed, with 40.12% (n=132), followed by tablets or capsules, with 34.95% (n=115).

Patients who took rivaroxaban and enoxaparin had a higher hospital discharge rates (n=65; 92.9%; p=<0.001 and n=221; 76.2%; p=<0.001, respectively), and the use of heparin had a higher relationship with death (n=86; 59.3%; p=<0.001) (Table 3). The dispensing of hydroxychloroquine and heparin was more frequent in the first wave (n=7; 4.9%; p=0.033 and n=74; 51.7%; p=0.001, respectively) (Table 4). In the second wave, there was an increase in the dispensing of rivaroxaban (n=57; 26.8%; p=<0.001), dexamethasone (n=189; 88.7%; p=<0.001), and azithromycin (n=94; 44.1%; p=0.019).

The antimicrobials most consumed in the first wave were polymyxin B sulfate, with 56.58 DDD/100 beds/day, and azithromycin, with 42.56 DDD/100 beds/day. In the second wave, the antifungal amphotericin B stands out, with 72.10 DDD/100 beds/day, followed by azithromycin, with 44.5 DDD/100 beds/day (Table 5).

Table 3. Association between outcome and prescription of anticoagulants, corticosteroids, azithromycin, hydroxychloroquine, ivermectin and colchicine during hospitalization for COVID-19

(Continua)

		Hospital discharge (n=257)		Death (n=99)		*p*
Medication	**Prescription**	n	%	n	%	
Colchicine[a]	No	254	72.2	98	27.8	0.691
	Yes	3	75.0	1	25.0	
Hydroxychloroquine[a]	No	249	71.8	98	28.2	0.450
	Yes	8	88.9	1	11.1	
Ivermectin[b]	No	215	71.8	84	28.1	0.910
	Yes	42	73.7	15	26.3	
Rivaroxaban[b]	No	192	67.1	94	32.9	<0.001*
	Yes	65	92.9	5	7.1	

(Conclusão)

Enoxaparin[b]	No	36	55.4	29	44.6	0.001*
	Yes	221	76.2	69	23.8	
Heparin[b]	No	171	81.0	40	19.0	<0.001*
	Yes	86	59.3	59	40.7	
Dexamethasone[b]	No	46	71.9	18	28.1	0.531
	Yes	211	72.3	81	27.7	
Methylprednisolone[b]	No	201	75.0	67	25.0	0.054
	Yes	56	63.6	32	36.4	
Azythromycin[b]	No	131	72.8	49	27.2	0.895
	Yes	126	71.6	50	28.4	

Legend: * Statistical significance considered p ≤ 0.050.[a] The Fischer's test; [b] Yates continuity correction test.

Table 4. Association between the pandemic period and prescription of anticoagulants, corticosteroids, azithromycin, hydroxychloroquine, ivermectin and colchicine during hospitalization for COVID-19

		First wave (n=143)		**Second wave (n=213)**		*p*
Medication	**Prescription**	n	%	n	%	
Colchicine[a]	No	142	99.3	210	98.6	0.652
	Yes	1	0.7	3	1.4	
Hydroxychloroquine[a]	No	136	95.1	211	59.3	0,033*
	Yes	7	4.9	2	0.9	
Ivermectin[b]	No	116	81.1	183	85.9	0.288
	Yes	27	18.9	30	14.1	
Rivaroxaban[b]	No	130	90.9	156	73.2	<0.001*
	Yes	13	9.1	57	26.8	
Enoxaparin[b]	No	32	22.4	34	16.0	0.165
	Yes	111	77.6	179	84.0	
Heparin[b]	No	69	48.3	142	66.7	0.001*
	Yes	74	51.7	71	33.3	
Dexamethasone[b]	No	40	28.0	24	11.3	<0.001*
	Yes	103	72.0	189	88.7	
Methylprednisolone[b]	No	114	79.7	154	72.3	0.143
	Yes	29	20.3	59	27.7	
Azythromycin[b]	No	61	42.7	119	55.9	0.019*
	Yes	82	57.3	94	44.1	

Legend: * Statistical significance considered p ≤ 0.050.[a] The Fischer's test; [b] Yates continuity correction test.

Table 5. Antimicrobial consumption, expressed in DDD (defined daily dose) per 100 bed-days, of 356 patients hospitalized for a period equal to or greater than 48 hours between the first and second wave of COVID-19

Therapeutic Class	Antimicrobial	DDD/100 bed-days	
		First wave	Second wave
Aminoglycosides	Amikacin	6.43	3.96
	Gentamicin	0.00	4.10
Antifungals	Amphotericin B	0.00	72.10
	Anidulafungin	11.34	6.78
Carbapenems	Meropenem	7.69	8.59
Cephalosporins	Cefazolin	0.05	0.04
	Cefepime	2.74	2.97
	Cefotaxime	0.00	0.22
	Ceftazidime	0.35	0.00
	Ceftazidime + avibactam	0.00	0.16
	Ceftriaxone	0.22	0.01
	Cefuroxime	1.28	2.72
Triazole derivates	Voriconazole	4.94	1.88
	Fluconazole	9.52	10.16
Fluoroquinolones	Ciprofloxacin	0.79	0.23
	Levofloxacin	4.37	17.52
Glycopeptides	Vancomycin	4.93	4.83
Lincosamides	Clindamycin	0.58	0.09
Macrolides	Azithromycin	42.56	44.5
	Clarithromycin	0.00	0.58
Others	Linezolid	0.64	0.39
Penicillins	Ampicillin + sulbactam	0.10	0.10
	Oxacillin	3.06	8.51
	Piperacillin + tazobactam	0.26	0.27
	Amoxicillin + clavulanic acid	3.68	3.84
	Amoxicillin	0.20	0.05
	Ampicillin	0.18	0.14
Polymyxins	Polymyxin B sulfate	56.58	39.04
	Polymyxin E sulfate	11.41	13.08
Tetracyclines	Tigecycline	0.00	12.46

DISCUSSION

To the best of our knowledge, this is one of the first studies to provide data on the use of medications during the COVID-19 pandemic, covering outpatient, chronic, and in-hospital use. Among the main findings, we have: 1) Most patients in the sample used some chronic medication, and one-third had polypharmacy; 2) The use of medications for COVID-19 was carried

out by more than a third of patients; 3) Higher education, reduced kidney function, having two or more comorbidities, and being polymedicated were associated with previous use of medications for COVID-19; 4) Azithromycin was the most used medication on an outpatient basis; 5) Patients who required intensive care and died used more medications during hospitalization; 6) Days of hospitalization and days of intensive care showed a strong correlation with the number of medications used; 7) In the first wave, there was a higher dispensing of hydroxychloroquine and heparin compared to the second, and in the second wave, there was an increase in the dispensing of rivaroxaban, dexamethasone, and azithromycin.

The presence of a high number of comorbidities was observed in the sample, with a higher prevalence of hypertensive and endocrine diseases, corroborating the study carried out during the first wave of COVID-19 in Spain, in which hypertension and diabetes were the most common diseases and a Brazilian study, carried out in the interior of the state of Rio Grande do Sul, whose prevalence of comorbidities was greater than 60%.[3,19]

The use of medicines to prevent or treat COVID-19 is similar to national and international data. In a Brazilian cross-sectional study, 22.3% of patients self-reported having previously used medication for COVID-19, and 36.0% of these patients used more than one medication.[4] An observational study in Lazio, Italy, identified that 29.0% of patients were prescribed at least one medication for COVID-19 in the outpatient setting.[13]

The off-label use of medications with wide variability in the population follows the trend of the pandemic wave, as already described in other studies. [13] The prescription and use of medicines for COVID-19 received great credibility in Brazil, where their use began to be publicized and encouraged on social media by health professionals, public authorities, and official Internet pages of Health Secretariats, Ministry of Health, and the Federal Government as treatment alternatives for COVID-19.[20]At the heart of the issue was the so-called "early treatment" or "COVID-kit": a combination of medications without conclusive scientific evidence, which included hydroxychloroquine or chloroquine combined with azithromycin, ivermectin, and nitazoxanide, in addition to vitamin supplements. Ivermectin was used on an outpatient basis by 15.3% of our patients, while another Brazilian study found a prevalence of 54.3%.[4] These differences may be directly related to the period of each study, where the indiscriminate use of medications was more characteristic at the beginning of the pandemic when there were still no robust scientific publications to support official recommendations.

Studies described the prevalence of antibiotic use in the outpatient setting as ranging from 17.5% to 31.3%, of which approximately 70.0% were attributable to azithromycin.[13] Corroborating our findings, antimicrobials had the highest frequency of use before hospitalization, and azithromycin was described in almost 70.0% of medical records. However, since COVID-19 is a viral infection, there is no evidence of the effectiveness of azithromycin in treating the disease, in addition to the fact that indiscriminate use increases rates of microbial resistance and is recommended by Brazilian guidelines only in the presence or suspicion of bacterial infection.[8]

It was not possible to infer whether the medications were used based on medical prescription or as a result of self-medication due to retrospective collection. Self-medication is a frequent practice by patients during the pandemic, estimated between 44.7 and 49.0% by different authors, and motivated by previous habits, ease of access, financial condition, and fear of being infected with the coronavirus. [15,21,22]

About the chronic use of medications, two studies carried out in Brazil stand out: in the first, 47.2% of hospitalized patients were continuous

users, while in the second, the prevalence was 37.4%.[4,23]These data are lower than found in our study and are probably due to the highly complex characteristics of the patients.

The criticality of hospital care is closely related to the number of medications used. Patients who required intensive therapy used a higher number of medications. Complications such as the need for dialysis, the presence of VAP, and sepsis, and the prescription of symptomatic and prophylactic drugs for thromboembolic complications directly contributed to greater use, both in the ward and in intensive care.

Several authors report the relationship between polypharmacy and COVID-19. [6,24,25] We identified polypharmacy in 28.1% of patients, similar to the findings of a systematic review, whose overall prevalence in patients with COVID-19 was 34.6%.[25] Another systematic review identified associations between polypharmacy and negative clinical outcomes in patients with COVID-19 in five of seven studies, whose higher average number of medications was associated with morbidity and increased mortality, in addition to representing an independent risk factor for the occurrence of adverse drug reactions (ADRs).[24] Polypharmacy can create iatrogenic risks that lead to unfavorable consequences, such as adverse effects and drug interactions that increase patients' vulnerability to COVID-19.[2] During the pandemic, the inclusion of lesser-known medications in the COVID-19 therapeutic arsenal and the high turnover of medications due to availability made the safety of drug therapy even more fragile.[24]

The high consumption of antimicrobials during hospitalization, especially broad-spectrum ones, can be explained by previous experience with influenza superinfection, in addition to the high proportion of critically ill patients on mechanical ventilation.[27] Furthermore, the increased consumption of antifungals in the second wave may be a reflection of the higher use of antibiotics, which may have contributed to the increase in fungal infections in the period.[27] The higher consumption of dexamethasone in the second wave is probably due to scientific publications and Brazilian Guidelines that emerged in the period; however, there was an increase in the prescription of rivaroxaban, and ivermectin continued to be prescribed even with the non-recommendation and proven ineffectiveness.[9]

The study has some limitations. Due to observational and retrospective data collection, patient descriptive information may not have been recorded or be incomplete in electronic medical records. The list of previous and chronic medications was based on self-report by the patient and/or companion upon hospital admission, and there may be memory gaps or, in cases of transference and/or unconsciousness of the patient, there may be no information in the medical record. In this way, some information may be underestimated and may have caused errors in the interpretation of the results.

Regarding the strengths of the study, our data were collected from a database of real cases and after extensive reading and review of the medical records to extract detailed information on the patient's conditions. The presence of electronic medical records at all stages of hospital admission can be considered a facilitator for data extraction. All information was reviewed and validated by a second researcher. Given the extensive number of teaching hospitals with similar characteristics in the country, extrapolation can be considered to other Brazilian institutions, mainly because the treatment for COVID-19 proposed in both waves was widely disseminated to society.

As future proposals, studies that identify problems related to pharmacotherapy (need, adherence, effectiveness, and safety) that occurred during the pandemic period can provide important data for patient care. In this context, the indiscriminate use of medicines during the pandemic highlights the need for patient education for disease prevention and

health management. Furthermore, in a public health context, measuring the cost related to the use of medicines in different patient profiles can be interesting to support the management of healthcare inputs and optimize the use of resources.

CONCLUSION

A high number of patients used medication to prevent or treat symptoms of COVID-19, while the majority were already on chronic medications, with polypharmacy present in almost a third of patients. Hypertensive and endocrine diseases prevailed. Differences were detected between the medications dispensed in each period and the outcome. However, it cannot be inferred whether the use is related to COVID-19 or due to pre-existing illnesses. The results found to elucidate the study hypothesis and provide relevant information about the use of medicines, weaknesses in health care, and the need for national policies that guide the safe use of medicines of COVID-19, promoting patient access to care and adequate health education.

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