

Drug Interactions in Patients with Previous Metabolic Syndrome Hospitalized with COVID-19: a Multifactorial Analysis



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Submission: November 06, 2025; **Published:** November 19, 2025

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Abstract

The COVID-19 pandemic has had significant impacts on global public health. Non-communicable chronic diseases, including Metabolic Syndrome, have intensified the risk of severe clinical complications, increasing the likelihood of hospitalizations. Furthermore, the widespread use of polypharmacy increases the risk of drug interactions that may worsen patients' conditions, highlighting the complexity of care. Further studies are needed to support effective clinical strategies. Objective: In this context, the present study aimed to analyze sociodemographic data and drug interactions present in patients with COVID-19 and Metabolic Syndrome, hospitalized in a teaching hospital located in the interior of Rio Grande do Sul, Brazil. Methods: The sample analyzed included patients over 18 years of age, of both sexes, hospitalized from March 2020 to May 2022, totaling 39 medical records. Results: Based on this sample, white married women predominated, with an average age of around 60 years, low educational level, polypharmacy, hospitalized for an average of 14 days, with hospital discharge in most cases. Prolonged hospitalization correlated positively with an increase in drug interactions. Moreover, the prescription of a greater number of medications during hospital discharge reinforces the need to recognize the complexity of the clinical picture and drug treatment. Conclusion: Therefore, the importance of prioritizing clinical management and adopting an individualized approach in the care of hospitalized patients with this infection and multiple comorbidities is evidenced.

Keywords: COVID-19; Metabolic Syndrome; Drug Interactions; Public Health; Hospitalization

Abbreviations: NCDs: Non-Communicable Chronic Diseases; MS: Metabolic Syndrome; WHO: World Health Organization; UFSM: University of Santa Maria; ATC: Anatomical Therapeutic Chemical; ICUs: intensive care units

Introduction

COVID-19, caused by the SARS-CoV-2 virus, is a highly contagious disease that has led to a series of challenges, impacting the healthcare system, the economy, and society as a whole [1]. Among the main factors contributing to the worsening of the pandemic, it is possible to highlight the high transmission rate of the virus through respiratory droplets, lack of effective treatment, insufficient resources, systemic inflammation associated with the disease, the presence of non-communicable chronic diseases (NCDs), population aging, and the absence of population immunity [2,3].

NCDs have resulted in a high number of premature deaths, reduced quality of life, and negative impacts on individuals [3]. Metabolic Syndrome (MS) can be considered one of the pathways leading to the development of NCDs, as it is characterized by a cluster of metabolic risk factors, including abdominal obesity, hypertension, elevated glucose levels, and other factors that increase the risk of developing cardiovascular diseases, type 2 diabetes mellitus, and other related conditions [4,5].

Individuals with MS have shown a higher risk of severe complications following coronavirus infection. Chronic

inflammation and impaired immune responses associated with MS may contribute to disease progression, leading to cardiovascular complications such as thrombosis, as well as respiratory problems due to systemic inflammation [6-9]. Therefore, considering this chronic disease status, the use of polypharmacy to manage MS and associated conditions is evident [10].

Studies have reported that the pandemic resulted in a significant increase in hospitalizations, particularly among polymedicated patients, who are at greater risk due to potential drug-drug interactions between COVID-19 treatments and their existing medications [10]. This is highly relevant, as such interactions may affect drug efficacy and increase the risk of adverse effects [11].

The events arising from the pandemic underscored the importance of preparing healthcare services for future public health emergencies [12,13]. Interprofessional collaboration among healthcare professionals proved essential to ensuring that patients receive individualized and safe care, taking into account pre-existing conditions and specific therapies [14].

Thus, to support healthcare providers in better understanding the clinical challenges faced by patients through the assessment of drug-drug interactions-facilitating therapy optimization, risk minimization, and improved patient outcomes-this study aimed to describe the sociodemographic and clinical characteristics of individuals with COVID-19 and MS admitted to a teaching hospital in the countryside of Rio Grande do Sul, Brazil, and to analyze the drug-drug interactions identified in this population.

Methods

Study Design and Population

This was a retrospective descriptive study of medical records from patients hospitalized in a teaching hospital in the countryside of Rio Grande do Sul, Brazil, with a confirmed diagnosis of COVID-19 and Metabolic Syndrome (MS) between March 2020 and May 2022. Initially, a database containing 664 records of patients hospitalized with COVID-19 was collected, in accordance with World Health Organization (WHO) guidelines and confirmed by positive RT-PCR results from nasopharyngeal and oropharyngeal swab samples [15].

Inclusion criteria comprised adult patients (≥ 18 years) and those with conditions related to metabolic syndrome (obesity, arterial hypertension, and diabetes mellitus). After screening, 47 medical records met the inclusion criteria. However, eight were excluded due to inconsistencies or incomplete information, resulting in a final sample of 39 medical records. This study was approved by the Research Ethics Committee of the Federal University of Santa Maria (UFSM) under CAAE number 52260621.3.0000.5346.

Study Variables

Data collection was performed using the electronic medical

record system known as the University Hospital Management Application (AGHU). The data collection period extended from November 2021 to July 2022, totaling eight months of retrospective extraction covering 26 months of the pandemic (March 2020 to May 2022). Sociodemographic data were collected, including sex, age, ethnicity, marital status, education level, and city of residence, as well as information on comorbidities, smoking and alcohol consumption habits, medications used at hospital admission and discharge, and hospitalization outcomes. Data were recorded in an Excel spreadsheet for subsequent analysis.

Medications prescribed at admission and discharge were categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System [16], internationally recognized by the WHO as the standard for drug utilization studies.

Data Analysis

Drug-drug interactions between medications used before and after hospitalization were evaluated. Interactions were identified using UpToDate® and classified according to interaction severity as X (contraindicated/severe), D (major), or C (moderate/minor) [17].

Statistical analyses were performed using GraphPad Prism® version 5 (GraphPad Software Inc., San Diego, CA, USA). Normality was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean (standard deviation) for normally distributed data and median (interquartile range) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages.

Comparisons of medication use frequencies between admission and discharge were conducted using Fisher's Exact Test. Comparisons of non-parametric data across time-points were performed using the Wilcoxon test. Drug interaction analyses were conducted using the Chi-Square test. Correlations were assessed using Pearson's coefficient (parametric data) or Spearman's coefficient (non-parametric data) and classified as weak ($r = 0.10-0.39$), moderate ($r = 0.40-0.69$), or strong ($r = 0.70-1.00$). Statistical significance was set at $p < 0.05$.

Results

The COVID-19 pandemic and its impacts highlighted the importance of understanding patient profiles and appropriately managing the specific needs of each population in an effort to prevent the worsening of potential future public health emergencies. In this context, it is essential to examine the sociodemographic data of patients and the clinical characteristics of hospitalizations that occurred during this period.

(Table 1) presents the demographic characteristics of the study sample, demonstrating a predominance of white, married women, with a mean age of approximately 60 years, incomplete primary education, and mostly residing in the central region of the state, where this study was conducted.

Table 1: Profile of hospitalized COVID-19 patients with metabolic syndrome in a university hospital in Rio Grande do Sul, Brazil, from 2020 to 2022.

Characteristics	N ¹ =39	% ²	Mean ±DP ³
Sex			
Female	24	61.54	
Male	15	38.46	
Age (years)			59.58 ± 11.45
Ethnicity			
White	35	89.75	
Black	1	2.56	
Brown/mixed race	2	5.13	
Not reported	1	2.56	
Marital status			
Married	19	48.72	
Single	9	23.08	
Widowed	9	23.08	
Divorced	1	2.56	
Not reported	1	2.56	
Educational level			
Incomplete primary education	18	46.15	
Complete primary education	6	15.39	
Incomplete secondary education	1	2.56	
Complete secondary education	5	12.82	
Higher education	2	5.13	
Not reported	7	17.95	
Place of residence			
Santa Maria	21	53.85	
Júlio de Castilhos	4	10.26	
São Pedro do Sul	3	7.69	
Outros	11	28.2	

¹N (Absolute Frequency), ²% (Relative Frequency), ³DP (Standard Deviation).

Regarding medical history, the data in Table 2 show that 20.51% of the sample were smokers and 25.64% were alcohol users, with chronic obstructive pulmonary disease (12.82%) being the most frequent comorbidity. Additionally, with respect to clinical outcomes, the median length of hospital stay was 14 days, and 53.85% of patients were discharged from the hospital.

Table 2: Clinical history, comorbid conditions, and outcomes of COVID-19 patients with metabolic syndrome admitted to a teaching hospital in Rio Grande do Sul, Brazil (2020-2022).

Characteristics	N ¹ =39	% ¹
Past medical history		
Alcohol use	10	25.64
Tobacco use	8	20.51
Comorbidities		
Chronic obstructive pulmonary disease	5	12.82
Heart failure	3	7.69
Heart failure	3	7.69
Stroke	3	7.69
Chronic kidney disease	3	7.69
Hereditary degenerative diseases of the nervous and muscular systems	2	5.13
Aortic/large vessel disease and arteriovenous fistulas	2	5.13
Asthma and bronchopulmonary dysplasia	2	5.13
Neoplasms	2	5.13
Liver disease and/or hepatic cirrhosis	1	2.56
Cardiac arrhythmias	1	2.56
Valvular heart disease	1	2.56
Other diseases	6	15.38
Clinical outcomes		
Length of hospital stay, median (IQR ³)	14 (6-24)	
Hospital discharge	21	53.85
Death	18	46.15

¹N (Absolute Frequency), ²% (Relative Frequency), ³IQR (Interquartile range - value expressed as median).

In Table 3, it is possible to observe the association between the use of different classes of medications and hospital admission and discharge outcomes. The use of oral and injectable hypoglycemic agents, antihypertensive drugs and diuretics, as well as lipid-lowering medications, was significantly associated with hospital discharge.

Table 3: Medications used at hospital admission and discharge in COVID-19 patients with metabolic syndrome, according to the ATC Classification System (2020-2022).

Medications	Hospital admission	Hospital discharge	p value
Antacids	3	4	1.0001
Antibiotics	2	1	0.6151
Antidepressants and anxiolytics	13	12	1.0001
Antihypertensives	20	11	<0.051*
Antihistamines	1	1	1.0001
Anti-inflammatory agents	8	4	0.3471
Antithrombotic agents	3	7	0.3101
Respiratory system medications	3	9	0.1141
Calcium channel blockers	15	11	0.4721
Diuretics	15	6	<0.051*
Lipid-lowering agents	13	4	<0.051*
Oral and injectable hypoglycemic agents	36	15	<0.0001***
Hormones	3	1	0.6151
Urological medications	1	5	0.2001
Muscle relaxants	1	1	1.0001
Vitamins and mineral supplements	3	5	0.7111
Total	2 (1-6)	1 (0-2.5)	0.0732

Values expressed as median (interquartile range) or frequency and percentage. 1 Fisher's Exact Test. 2 Wilcoxon Test. * p<0.05, ** p<0.0001.

Table 4: Classification of drug-drug interactions at admission and discharge in COVID-19 patients with metabolic syndrome (2020-2022).

Drug interaction period	X	D	C	² Total
Hospital admission	0	5	32	37
Hospital discharge	1	3	27	31
¹ Total	1	8	59	68

X (avoid combination), D (consider therapy modification), C (monitor therapy), ¹Total total drug interactions by degree of interaction), ²Total (total drug interactions by period).

Table 4 presents the number of drug-drug interactions identified in each period based on the severity classification obtained through UpToDate® analysis. Most interactions occurred during the hospital admission period, predominantly classified as grade C, indicating that monitoring of therapy was recommended. The only severe interaction identified was between metoclopramide and quetiapine at hospital discharge. The medications most frequently associated with interactions were hydrochlorothiazide, dipyrone (metamizole), risperidone,

quetiapine, diazepam, amitriptyline, and cyclobenzaprine.

Table 5 presents a detailed analysis of the correlations between variables of interest in patients hospitalized with COVID-19, including data related to clinical management and outcomes. Regarding length of hospital stay, a positive correlation ($r = 0.318$) was observed with the number of medications prescribed at hospital discharge, suggesting that a longer hospitalization period is associated with a higher number of medications at discharge.

Table 5: Correlation analysis of key study variables.

Variables	Values
Length of hospital stay	
Number of comorbidities	$p < 0.05$; $r = -0.348^*$
Number of medications at admission	$p = 0.343$; $r = -0.156$
Number of medications at discharge	$p < 0.05$; $r = 0.318^*$
Number of drug interactions at admission	$p = 0.613$; $r = -0.083$
Number of drug interactions at discharge	$p = 0.225$; $r = 0.199$
Age	$p = 0.093$; $r = -0.272$
Discharge/death	$p = 0.054$; $r = 0.311$
Number of comorbidities	
Number of medications at admission	$p = 0.115$; $r = 0.256$
Number of medications at discharge	$p = 0.882$; $r = 0.025$
Number of drug interactions at admission	$p = 0.177$; $r = 0.220$
Number of drug interactions at discharge	$p = 0.635$; $r = -0.078$
Age	$p = 0.227$; $r = 0.198$
Discharge/death	$p = 0.576$; $r = 0.092$
Number of medications at admission	
Number of drug interactions at admission	$p < 0.0001$; $r = 0.819^{**}$
Number of drug interactions at discharge	$p = 0.171$; $r = 0.224$
Number of medications at discharge	
Number of drug interactions at admission	$p = 0.751$; $r = 0.052$
Number of drug interactions at discharge	$p < 0.0001$; $r = 0.739^{**}$
Discharge/death	
Age	$p = 0.056$; $r = 0.309$
Number of drug interactions at admission	$p = 0.376$; $r = 0.156$
Number of drug interactions at discharge	$p = 0.483$; $r = 0.116$

Pearson correlation or Spearman correlation. * $p < 0.05$, ** $p < 0.0001$.

With respect to the number of medications at admission, a highly significant and positive correlation was identified ($p < 0.0001$; $r = 0.819$) with the number of drug-drug interactions during hospitalization. Additionally, considering the number of medications at discharge, there was a significantly positive correlation ($p < 0.0001$; $r = 0.739$) with the number of drug-drug interactions at admission, emphasizing the persistence of these interactions across different periods of hospitalization.

Discussion

The presentation of demographic characteristics in this study highlights the importance of understanding patient diversity when analyzing outcomes and associations in this type of research. The predominance of women in this sample differs from findings in other studies [18,19]. However, this discrepancy may be attributed to the high prevalence of metabolic syndrome among women, particularly those over 50 years of age, which may be influenced by hormonal and genetic factors [20].

The mean age of participants was approximately 60 years, consistent with studies that emphasize aging as an important factor in metabolic deterioration, characterized by the accumulation of risk factors, including chronic diseases, and even influencing drug tolerance and therapeutic responses [18]. The ethnic composition of the sample, mostly White individuals (89.75%), contrasts with the predominance of COVID-19 among Black populations reported in the literature [21].

Regarding marital status, most participants were married (48.72%). Previous studies suggest that married individuals may benefit from stronger emotional and social support, potentially influencing treatment adherence, recovery from medical conditions, and overall health outcomes [22]. Additionally, 46.15% of the sample had incomplete primary education, corroborating evidence that lower education levels are associated with reduced understanding of health information, limited self-management ability, and an increased likelihood of developing chronic diseases such as diabetes mellitus, which may limit daily living activities [23,24].

Another relevant finding is the participants' place of residence: most lived in the city where the study was conducted (53.85%), while the remainder came from other municipalities or states. This highlights the importance of considering regional and geographic characteristics in health status and access to healthcare services. During the pandemic, equitable distribution of services, professionals, and equipment posed significant challenges, leading many patients to travel long distances seeking hospitalization, an unfavorable situation given the rapid progression of the disease [25].

In terms of prior medical history, smoking and alcohol consumption were observed in the sample, factors known to negatively affect health. Previous studies have shown a correlation between smoking, excessive alcohol use, and various

health conditions, including cardiovascular, respiratory, and liver diseases [26]. Identifying these behavioral risk factors underscores the importance of addressing them during treatment and incorporating them into care strategies.

Comorbidities observed in this study (chronic obstructive pulmonary disease, heart failure, coronary syndromes, stroke, and chronic kidney disease) align with evidence that these conditions are highly prevalent among hospitalized patients. This underscores the complexity of managing these patients and the need for an interdisciplinary healthcare team [27,28].

Regarding clinical outcomes, the findings are consistent with studies involving hospitalized patients with complex health conditions [27]. The median length of stay of 14 days suggests variability in hospitalization duration, possibly related to the severity of comorbidities, recovery time, and the fact that individuals with pre-existing conditions are more likely to develop severe COVID-19 [28]. Hospital discharge occurred in 53.85% of cases, indicating positive recovery and reflecting the healthcare team's efforts and effectiveness of clinical interventions, including respiratory management and medical support [8,9,14].

However, the mortality rate of 46.15% is alarming, highlighting the lethality of COVID-19 and the need for appropriate interventions. Our findings support evidence that women over 50 years old with comorbidities have a greater likelihood of prolonged hospitalization and higher mortality [29]. Furthermore, patients with severe COVID-19 admitted to intensive care units (ICUs) experience significant morbidity and mortality, often requiring intensive support and prolonged hospitalization [30].

Most drug-drug interactions identified at admission and discharge were classified as mild, contrasting with studies reporting a higher number of severe interactions [31]. Only one severe interaction was identified, involving metoclopramide and quetiapine, which may potentiate toxicity and lead to extrapyramidal symptoms or neuroleptic malignant syndrome.

Investigating the relationship between medication use and hospitalization outcomes in COVID-19 patients is crucial given the clinical complexity of this disease. Results demonstrated an association between certain medication classes and hospital discharge, particularly antihypertensive, diuretic, lipid-lowering, and hypoglycemic agents. Given the presence of metabolic syndrome in these patients, careful management of blood pressure and lipid levels during COVID-19 treatment is essential, particularly considering circulatory decompensation caused by the infection [32].

Conversely, no significant association was observed between hospital discharge and other medication classes evaluated. However, research indicates that anxiety, depression, chronic pain, and respiratory problems may persist after COVID-19, affecting quality of life [33-36].

A significant association was found between the number of medications, drug-drug interactions, and length of stay, emphasizing the need for careful monitoring of interactions in patients using multiple drugs, as they may affect treatment safety and efficacy [37]. In this context, the pharmacist's role is essential, as their expertise contributes to reducing risks related to drug interactions through dosage adjustments, administration timing, dilution recommendations, route adjustments, and other interventions [38]. It is important to note that few medical records included pharmaceutical anamnesis or follow-up, despite evidence of the value of pharmacist involvement in inpatient care.

Conclusion

This study confirmed the complexity of factors involved in COVID-19 infection, particularly among patients with pre-existing comorbidities. It demonstrated the importance of analyzing sociodemographic and clinical history, as these factors affect clinical outcomes during hospitalization.

In this study, most patients were White women, married, around 60 years of age, with low educational attainment, using multiple medications, and hospitalized for a median of 14 days, with most being discharged. The number of medications was significantly associated with drug-drug interactions and length of stay. Additionally, our analysis demonstrated the positive impact of antihypertensives, diuretics, lipid-lowering agents, and hypoglycemic medications on hospital discharge, with important implications for improving clinical outcomes.

Therefore, it is essential to prioritize clinical management and individualized care for hospitalized patients with COVID-19 and multiple comorbidities and pharmacotherapies. The pharmacist's role is particularly relevant, contributing to minimizing risks related to drug-drug interactions. The findings and correlations identified here may support clinical decision-making and enhance care quality for patients with metabolic syndrome hospitalized with COVID-19. These findings may aid in understanding disease progression among patients with chronic conditions and encourage future research, ultimately supporting the advancement of clinical guidelines.

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DOI: [10.19080/GJPPS.2025.12.555833](https://doi.org/10.19080/GJPPS.2025.12.555833)

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