ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH DEATH BY COVID-19 IN A UNIVERSITY HOSPITAL IN SOUTHERN BRAZIL: A CROSS-SECTIONAL STUDY

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Highlights: (1) Cross-sectional research with retrospective data collection from hospitalized patients. (2) Greater deaths among institutionalized elderly and dialysis patients. (3) No significant difference in deaths between the first and second waves.

PRE-PROOF

(as accepted)

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ABSTRACT

This is a cross-sectional study with retrospective data collection that analyzed 356 patients admitted to a university hospital that serves as a reference for severe cases of COVID-19 during the first and second waves in Rio Grande do Sul, Brazil. Mortality was the outcome of interest, and significant variables were subjected to Poisson regression. Ninety-nine patients (27.8%) had death as an outcome. Low education, admission in poor general condition, malnutrition, lack of prior diagnosis of COVID-19, the presence of symptoms other than flu or respiratory symptoms, and polypharmacy were more common in patients who died. Reduced glomerular filtration rate, D-Dimer, C-reactive protein, urea, and elevated International Normalized Ratio were found upon hospital admission in patients who died. No differences were found in deaths between periods of the pandemic. After multivariate analysis, the factors related to death, in decreasing order of prevalence, were institutionalization, prolonged mechanical ventilation (>21 days) or for up to 21 days, high International Normalized Ratio on admission, age over 65 years, need for dialysis, and acute respiratory insufficiency. The results help to understand the behavior of the disease and provide support for training and resource allocation in scenarios of exponential care demands, such as outbreaks and epidemics.

Palavras-Chave: COVID-19, Epidemiology, Brazil, University Hospitals, Mortality.

INTRODUCTION

In 2019, severe acute respiratory syndrome caused by coronavirus (SARS-CoV-2) spread rapidly to all countries and territories, turning into a COVID-19 disease pandemic, with case fatality reports ranging from 1 to 7% of cases [1,2]. In Brazil, by May 2023, more than 37 million infected people had been recorded, with more than 700 thousand deaths from COVID-19 and a case fatality rate of 2%[3,4]. Specifically in the state of Rio Grande do Sul (RS), by May 2023, more than 3 million infected people and 42 thousand deaths had been recorded, with a case fatality rate of 1.4%, placing it in the 5th position in the number of deaths and 10th position in the mortality rate from SARS-CoV-2 per 100 thousand inhabitants among the 27 federative units of Brazil[3,5].

A study conducted in Brazil during the first and second waves identified that RS is one of the states with the highest rates of hospitalization in hospital beds and intensive care units (ICUs) per 100 thousand inhabitants, with about 120 thousand people requiring hospitalization[5,6]. The association of demographic data, clinical characteristics, use of medications, and disease outcome according to the progression of the COVID-19 pandemic is a way to identify the risk factors for hospitalization and mortality from SARS-CoV-2[7]. Direct and indirect variables can impact the outcome of the disease, as in Brazil, where in the first and second year of the pandemic, there were several outbreaks, uncontrolled dissemination, lack of resources, use of drugs without proven efficacy, among other factors that may have influenced the course of the disease[8].

The assessment of the most common risk factors for mortality, length of hospital stays, and outcomes of COVID-19 becomes crucial to guide health professionals in decision-making, evaluate the course of infection, and improve health outcomes[7]. In this context, Brazil is an important and interesting country to study the impact of COVID-19, in part due to the combination of the severity of the outbreak, the government's failure to implement non-pharmaceutical interventions, and the complex social and ethnic composition of society[9]. This scenario, combined with the regional disparities found in Brazil and especially in the southern region, leads to the need to elucidate the hypothesis that there are certain sociodemographic and clinical characteristics that are related to the death of patients with COVID-19 hospitalized in RS.

The objective of this study is to analyze the clinical-epidemiological characteristics correlating with the mortality observed in patients hospitalized for COVID-19 for 48 hours or more in a university hospital in Porto Alegre, RS, Brazil.

METHODS

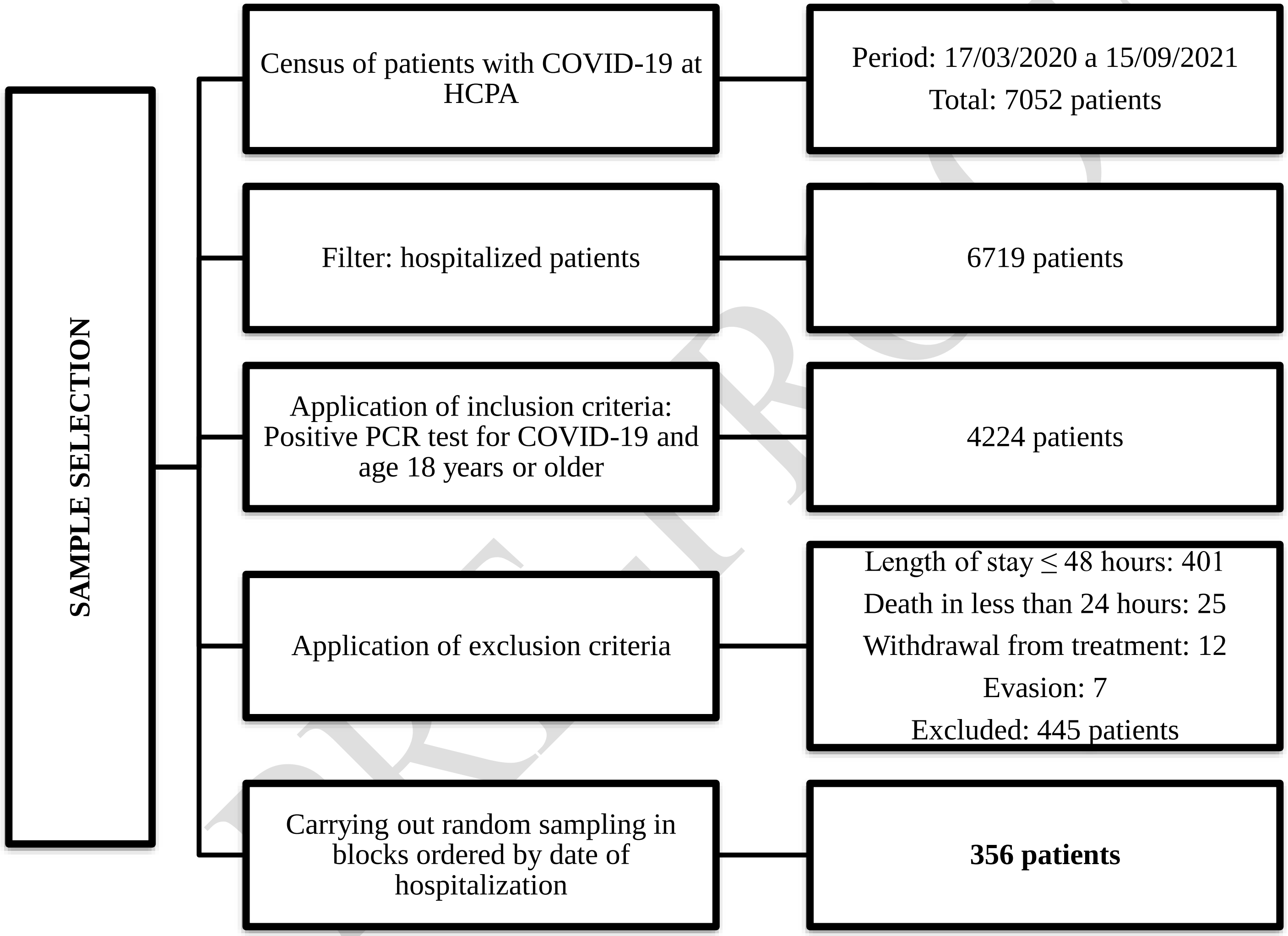
Research location

The Hospital de Clínicas de Porto Alegre (HCPA) is a public, general university hospital, accredited by the Joint Commission International. During the coronavirus pandemic, it was one of the reference centers in high-complexity COVID-19 care and had the largest number of intensive care beds in RS, reaching 105 beds during the period of greatest severity of the disease in RS[10]. Located in the capital of Rio Grande do Sul, the hospital belongs to the metropolitan macro-region and the 10th health micro-region of the state. Overall, it has a total of 836 beds. By the end of 2021, 7,436 patients with COVID-19 had been admitted to the HCPA[5,10].

Study design

An analytical, observational, and cross-sectional study was carried out, with retrospective data collection, based on the analysis of data from the medical records of patients hospitalized with coronavirus infection at the HCPA. Based on the list of 4,224 hospitalized patients with a positive Polymerase Chain Reaction (PCR) laboratory test for SARS-CoV-2, a sample size calculation was performed using the WINPEPI® software (Figure 1). Considering a maximum absolute error of 0.05, a variability of 0.5, and a confidence interval of 95%, a sample of at least 356 medical records was required for analysis. After ordering the medical records by date of hospitalization, random sampling was systematically carried out in blocks. Clinical-epidemiological data were extracted from the HCPA Biobank[11] database, and data that could not be extracted through reports from the computerized system were actively collected from the review of the information recorded in the electronic medical record..

Figure 1 – Descriptive flowchart of the steps for selecting the patient sample.



Inclusion and exclusion criteria

The inclusion criteria for the study were patients aged 18 years or older, hospitalized between March 17, 2020 – the date that corresponds to the first patient diagnosed with COVID-19 at the HCPA – and September 15, 2021. The time period from March to November 2020 was considered the first wave of COVID-19 in RS, and after December 2020, as the period of the second wave. Patients with the following characteristics were not included: death in less than 24 hours, hospital stays of less than 48 hours, reason for hospitalization unrelated to COVID-19, incomplete or inconsistent data in the electronic medical record, and/or unknown health outcome due to dropout, transfer to other health institutions, or hospitalization not yet completed at the time of analysis.

To control for potential biases and confounding factors, the selection of cases was based on ordering by the date of hospitalization and random selection (by sampling) of the selected medical records. Information bias was minimized by excluding medical records with incomplete information. The patient's recall bias and state of consciousness at the time of admission may have underestimated some variables. Confounding factors were minimized through regression modeling.

Study variables

The selected independent variables refer to the following data:

Demographic and epidemiological data: gender, age, race, institutionalization, education, geographic region of residence in RS, origin or source of origin (from where the patient came to admission, classified as spontaneous demand, primary or outpatient care, mobile emergency care service, or transfer between hospitals) and therapeutic itinerary (health services sought by the patient for the treatment of COVID-19 before requiring hospitalization).

Clinical history: general status of the patient (GSP) – subjective assessment carried out by the health professional regarding the general appearance of the patient's health status, where the normality of vital signs and level of consciousness are generally assessed[12]; history of contagion; comorbidities; body mass index (BMI) – calculated by dividing the individual's weight in kilograms by the square of their height in meters[13], having been classified into as follows: <18.49 as malnourished; 18.50-24.99 as eutrophic; 25.00-29.99 as overweight; and

>30 kg/m² as obese –; oxygenation at admission; smoking history; and immunization against COVID-19 – considered only for patients hospitalized on or after January 18, 2021, the date that marked the beginning of vaccine distribution in RS, regardless of the number of doses received.

Laboratory information at hospital admission: glomerular filtration rate (eGFR) – calculation performed according to the Collaboration Equation in Epidemiology of Chronic Kidney Disease (CKD-EPI)[14], D-dimer, C-reactive protein (CRP), urea, liver enzymes, and coagulogram.

Complications during hospitalization: pulmonary thromboembolism (PTE), deep vein thrombosis (DVT), need for an intensive care bed, sepsis, acute respiratory failure (ARI), delirium, and ventilator-associated pneumonia (VAP). Days of mechanical ventilation were segregated into two categories – up to 21 days or more than 22 days, with time longer than 21 days being classified, according to the Brazilian Guidelines on Mechanical Ventilation[15], as prolonged mechanical ventilation. Intensive care days were classified into two categories – up to 7 days or above 8 days. The division was made based on the average length of stay in the ICU of a public hospital which is 6.55 days[16].

Therapeutic interventions during hospitalization: thoracostomy, convalescent plasma, tracheostomy, extracorporeal membrane oxygenation (ECMO), and dialysis.

In-hospital mortality was the outcome of interest.

Statistical analysis

The data were tabulated in a Microsoft Excel spreadsheet and then submitted to statistical analysis. Demographic and clinical data were described as proportions for categorical variables and as median and interquartile range for continuous variables. The normality of the quantitative data was assessed using the Shapiro-Wilks test. Categorical variables were compared using Fisher's exact test, Pearson's Chi-square test, or Yates' continuity correction test. Continuous variables were compared using Mann-Whitney U test for independent samples. Variables of clinical importance and with significance at the level of 5% ($p<0.05$) were submitted to bivariate Poisson multiple analysis regression with adjustment for robust variances and Wald's chi-square test. Prevalence ratios (PR) and Confidence Intervals (CI 95%)

were obtained, and the level of significance adopted was a p-value ≤ 0.05 in the Chi-square Likelihood Ratio test. Independent variables statistically associated with outcome at a level of $p \leq 0.05$ in the bivariate analysis were included in the multivariate analysis model. The level of statistical significance was 5% ($p \leq 0.050$). All analyses were performed using SPSS® version 18.0.

Ethical aspects

The project was approved by the Research Ethics Committee of the HCPA under opinion No. 4.672.349 and CAAE 44718021.3.0000.5327. The researchers declared that they were aware of and comply with the requirements of the General Data Protection Law (Law No. 13,709, of August 14, 2018) and signed the Data Use Commitment Agreement for the use of the COVID-19 Biobank, ensuring the confidentiality, secrecy, and privacy of patients and professionals. They also stated that there was no conflict of interest that could interfere with the impartiality of the research. The Individual Consent Form was waived due to the use of anonymized data based only on the review of medical records.

This article follows the guidelines of the Strengthening the reporting of observational studies in epidemiology (STROBE) for cross-sectional studies[17].

RESULTS

The records of 356 patients were analyzed, 40.2% (n=143) of whom were from the period of the first wave of COVID-19 and 59.8% (n=213) from the second wave. Regarding gender, 56.5% (n=201) were men and 43.5% (n=155) were women, with a median age of 62 years. Of these, 27.8% (n=99) died (Tables 1 and 2).

Table 1 - Distribution of quantitative variables compared in relation to the outcome of discharge or death. Data are presented as median and interquartile range 25-75%.

	Hospital discharge (n=257) Median (IIQ 25-75%)	**Death (n=99) Median (IIQ 25-75%)**	***p***
Age (n=356)	58,0 (44,5 – 69,0)	69,0 (59,0 – 76,0)	<0,001*
Total days of hospitalization (n=356)	11,9 (7,0 – 23,4)	17,9 (10,5 – 30,1)	0,005*
Days in hospital bed (n=302)	8,0 (5,0 – 12,0)	7,0 (2,0 – 14,7)	0,352
Days in intensive care unit (n=248)	8,0 (3,0 – 20,0)	16,0 (6,0 – 28,5)	0,001*
Mechanical ventilation days (n=167)	14,0 (7,0 – 25,0)	16,5 (10,7 – 29,2)	0,079
BMI (n=310)	29,6 (26,2 – 35,4)	28,4 (24,7 – 31,2)	<0,001*
Number of comorbidities (n=356)	2,0 (1,0 – 3,0)	3,0 (2,0 – 4,0)	0,037*
Laboratory data on admission			
eGFR (n=356)	79,5 (56,0 – 96,4)	43,5 (21,6 – 43,5)	<0,001*
D-Dimer (n=332)	1,0 (0,6 – 1,7)	2,1 (1,0 – 8,3)	<0,001*
CRP (n=352)	113,2 (65,5 – 176,4)	145,7 (95,2 – 259,2)	<0,001*
Urea (n=356)	37,0 (28,0 – 56,5)	75,0 (44,0 – 123,0)	<0,001*
GPT (n=338)	45,0 (30,0 – 63,5)	44,0 (30,7 – 64,5)	0,888
GOT (n=343)	44,0 (25,0 – 68,0)	31,0 (21,0 – 48,0)	0,001*
INR (n=341)	1,0 (1,0 – 1,1)	1,1 (1,0 – 1,3)	<0,001*

IIQ: interquartile range, BMI: Body Mass Index, SBP: systolic blood pressure, DBP: diastolic blood pressure, SpO^2: oxygen saturation, RR: respiratory rate, HR: heart rate, TA: axillary temperature, eGFR: filtration rate glomerular, CRP: C-reactive protein, TGP: glutamic pyruvic transaminase, TGO: oxaloacetic transaminase, INR: International Normalized Ratio. * Statistical significance considered $p \leq 0.050$.

Table 2 - Demographic, epidemiological and clinical profile of patients hospitalized with COVID-19 compared with the outcome of death or discharge of patients admitted with COVID-19 at the HCPA. Numbers are presented as absolute numbers and percentages (n=356).

		HOSPITAL DISCHARGE			**DEATH**			
		Variable		**∑ Variable**	**Variable**		**∑ Variable**	**p**
		n	**%**	**%**	**n**	**%**	**%**	
DEMOGRAPHIC AND EPIDEMIOLOGICAL DATA								
Sex (n=356)	Male	142	39,9	70,6	59	16,6	29,4	0,534
	Female	115	32,3	74,2	40	11,2	25,8	
Age (n=356)	Less than or equal to 65 years old	176[1]	49,4	81,9	39	11,0	18,1	<0,001* (a)
	Over 65 years old	81	22,8	57,5	60[1]	16,9	42,5	
Pandemic period (n=356)	First wave	95	26,7	37,0	48	13,5	48,5	0,062 (b)
	Second wave	162	45,5	63,0	51	14,3	51,5	
Race (n=356)	Caucasian	214	60,1	72,8	80	22,5	27,2	0,583 (c)
	Other races (black, brown, indigenous and yellow)	43	12,1	69,4	19	5,3	30,6	
Institutionalized (n=356)	Yes	0	0	0	6[1]	1,7	100	<0,001* (b)
	No	257[1]	72,2	73,4	93	26,1	26,6	
Education (n=356)	Basic education	115[1]	32,3	66,1	59[1]	16,6	33,9	0,027* (c)
	High school	82	23,0	80,4	20	5,6	19,6	
	University education	33	9,3	82,5	7	2,0	17,5	
	Unknown	27	7,6	67,5	13	3,7	32,5	
Health region (n=356)	Porto Alegre/Metropolitana	205	57,6	73,0	76	21,3	27,0	0,634 (a)
	Interior	52	14,6	69,3	23	6,5	30,7	
Origin								
Spontaneous demand (n=356)	Yes	162[1]	45,5	79,0	43	12,1	21,0	0,001* (a)
	No	95	26,7	62,9	56[1]	15,7	37,1	
Primary care or outpatient clinic (n=356)	Yes	4	1,1	50,0	4	1,1	50,0	0,309 (b)
	No	253	71,1	72,7	95	26,7	27,3	
MECS or transfer between hospitals (n=356)	Yes	91	25,6	63,6	52[1]	14,6	36,4	0,005*(b)
	No	166[1]	46,6	77,9	47	13,2	22,1	
Previous therapeutic itinerary								
Recent hospital discharge (n=356)	Yes	18	5,1	66,7	9	2,5	33,3	0,658 (a)
	No	239	67,1	72,6	90	25,3	27,4	
Outpatient care (n=356)	Yes	14	3,9	87,5	2	0,6	12,5	0,253 (b)
	No	243	68,3	71,5	97	27,2	28,5	
Primary care (n=356)	Yes	77	21,6	74,1	27	7,6	25,9	0,712 (a)
	No	180	50,6	71,5	72	20,2	28,5	
Hospital emergency (n=356)	Yes	117	33	75,5	38	10,7	24,5	0,305 (a)
	No	140	39,4	70,0	60	16,9	30,0	

Other hospital (n=356)	Yes	50	14,1	62,5	30[1]	8,5	37,5	0,042*(a)
	No	206[1]	58,0	75,0	69	19,4	25,0	
Private medical office (n=356)	Yes	4	1,1	80,0	1	0,3	20,0	1,000 (b)
	No	253	71,1	72,1	98	27,5	27,9	
CLINICAL DATA								
General Condition of the Patient upon admission (n=355)	GGC	83[1]	23,3	83,8	16	4,5	16,2	<0,001* (c)
	RGC	169	47,4	70,1	72	20,3	29,9	
	PGC	5	1,4	31,4	11[1]	3,1	68,6	
Initial symptoms and contagion history								
Flu symptoms (n=355)	Yes	85	23,9	76,6	26	7,3	23,4	0,255 (a)
	No	171	48,2	70,1	73	20,6	29,9	
Dyspnea (n=356)	Yes	131	36,8	76,2	41	11,5	23,8	0,134 (a)
	No	126	35,4	68,5	58	16,3	31,5	
Other symptoms (n=356)	Yes	37	10,4	55,2	30	8,4[1]	44,8	0,001* (a)
	No	220[1]	61,8	76,1	69	19,4	23,9	
COVID confirmed (n=356)	Yes	144[1]	40,4	77,4	42	11,8	22,6	0,029*(a)
	No	113	31,7	66,5	57[1]	16,0	33,5	
Close personal contact (n=355)	Yes	35	9,9	81,4	8	2,3	18,6	0,205 (a)
	No	221	62,3	70,8	91	25,6	29,2	
Complications during hospitalization								
Need for intensive care bed (n=356)	Yes	163[1]	45,8	65,7	85[1]	23,9	34,3	<0,001* (a)
	No	94[1]	26,4	87,0	14[1]	3,9	13,0	
Intensive care days (n=248)	1 to 7 days	78[1]	31,5	78,0	22	8,9	22,0	0,001* (a)
	8 or more	85	34,3	57,4	63[1]	25,4	42,6	
Need for mechanical ventilation (n=356)	Yes	89	25,0	53,3	78[1]	21,9	46,7	<0,001* (a)
	No	168	47,2	88,9	21	5,9	11,1	
Mechanical ventilation days (n=167)	1 to 21	62	37,1	56,9	47	28,1	43,1	0,267 (a)
	22 days or more	27	16,2	46,6	31	18,6	53,4	
PTE (n=355)	Yes	33	9,3	57,9	24[1]	6,8	42,1	0,014* (a)
	No	223[1]	62,8	75,0	75	21,1	25,2	
DVP (n=355)	Yes	10	2,8	55,6	8	2,3	44,4	0,181 (a)
	No	246	69,3	73,0	91	25,6	27,0	
Sepsis (n=354)	Yes	22	6,2	64,7	12	3,4	35,3	0,423 (a)
	No	233	65,8	72,8	87	24,6	27,2	
ARF (n=355)	Yes	47	13,2	46,1	55[1]	15,5	53,9	<0,001* (a)
	No	209[1]	58,9	82,6	44	12,4	17,4	
Delirium (n=355)	Yes	16	4,5	72,7	6	1,7	27,3	1,000 (a)
	No	240	67,6	72,1	93	26,2	27,8	

VAP (n=355)	Yes	40	11,3	52,6	36[1]	10,1	47,4	<0,001* (a)
	No	216[1]	60,8	77,4	63	17,7	22,6	
COVID Immunization (n=175)	Yes	22	12,6	81,5	5	2,9	18,5	0,581 (a)
	No	110	62,9	74,3	38	21,7	25,7	
Therapeutic interventions during hospitalization								
Thoracostomy (n=354)	Yes	3	0,8	25,0	9[1]	2,5	75,0	0,001* (b)
	No	252[1]	71,2	73,7	90	25,4	26,3	
Convalescent plasma (n=355)	Yes	3	0,8	75,0	1	0,3	25,0	1,000 (b)
	No	253	71,3	72,1	98	27,6	27,9	
Tracheostomy (n=355)	Yes	15	4,2	51,7	14[1]	3,9	48,3	0,019* (a)
	No	241[1]	67,9	73,9	85	23,9	26,0	
ECMO (n=355)	Yes	3	0,8	100	0	0	0	0,563 (b)
	No	253	71,3	71,9	99	27,9	28,1	
Dialysis (n=355)	Yes	21	5,9	30,4	48[1]	13,5	69,6	<0,001* (a)
	No	235[1]	66,2	82,2	51	14,4	17,8	
Oxygenation on admission (n=356)	Ambient air	167[1]	47,0	77,7	48	13,5	22,3	<0,001* (b)
	Oxygen therapy, NIV, HFNC or tracheostomy	73	20,6	75,3	24	6,8	24,7	
	Mechanical ventilation	16[1]	4,5	37,2	27[1]	7,6	62,8	
Smoking history (n=356)	Active or former smoker	60	16,9	65,2	32	9,0	34,8	0,110 (b)
	No	197	55,3	74,6	67	18,8	25,4	
BMI classification (n=310)	Malnutrition (>18,5 kg/m²)	9[1]	2,9	45,0	11[1]	3,5	55,0	0,030* (c)
	Eutrophic (18,50-24,99 kg/m²)	44	14,2	69,8	19	6,1	30,2	
	Overweight (25,00-29,99 kg/m²)	66	21,3	73,3	24	7,7	26,7	
	Obesity (>30 kg/m²)	105	33,9	76,6	32	10,3	23,4	
eGFR Classification (n=356)	Normal	90[1]	25,5	84,1	17	4,8	15,9	<0,001*(c)
	Mild to mild-moderate reduction	121[1]	34,3	78,6	33	9,3	21,4	
	Moderate-severe reduction in kidney failure	43	12,2	46,7	49[1]	13,9	53,3	
Presence of comorbidities (n=356)	None	50	14,0[1]	86,2	8	2,2	13,8	0,022* (c)
	One comorbidity	53	14,9	73,6	19	5,3	26,4	
	Two or more comorbidities	154	43,3	68,1	72[1]	20,2	31,9	
Use chronic medications	Yes	38	22,8	59,4	26	15,6	40,6	0,279 (b)
	No	51	30,5	49,5	52	31,1	50,5	
Features polypharmacy	Yes	75[1]	44,9	58,1	54	32,3	41,9	0,033* (b)
	No	14	8,4	36,8	24[1]	14,4	63,2	

Variable: % of occurrence among all outcomes. ∑ Variable: % of occurrence between a given outcome. MECS: Mobile Emergency Care Service, GGC: good general condition, RGC: regular general condition, PGC: poor general condition, PTE: pulmonary thromboembolism, DVP: deep venous thrombosis, ARF: acute respiratory failure, PAVM: ventilator-associated pneumonia, ECMO: extracorporeal membrane oxygenation, NIV: non-invasive ventilation, HFNC: high flow nasal cannula, BMI: body mass index, eGFR: estimated glomerular filtration rate. * Statistical significance considered $p \leq 0.050$; (a) Yates continuity correction test; (b) Fisher's exact test; (c) Pearson's Chi-square test; [1] Variable with significant association in relation to the outcome.

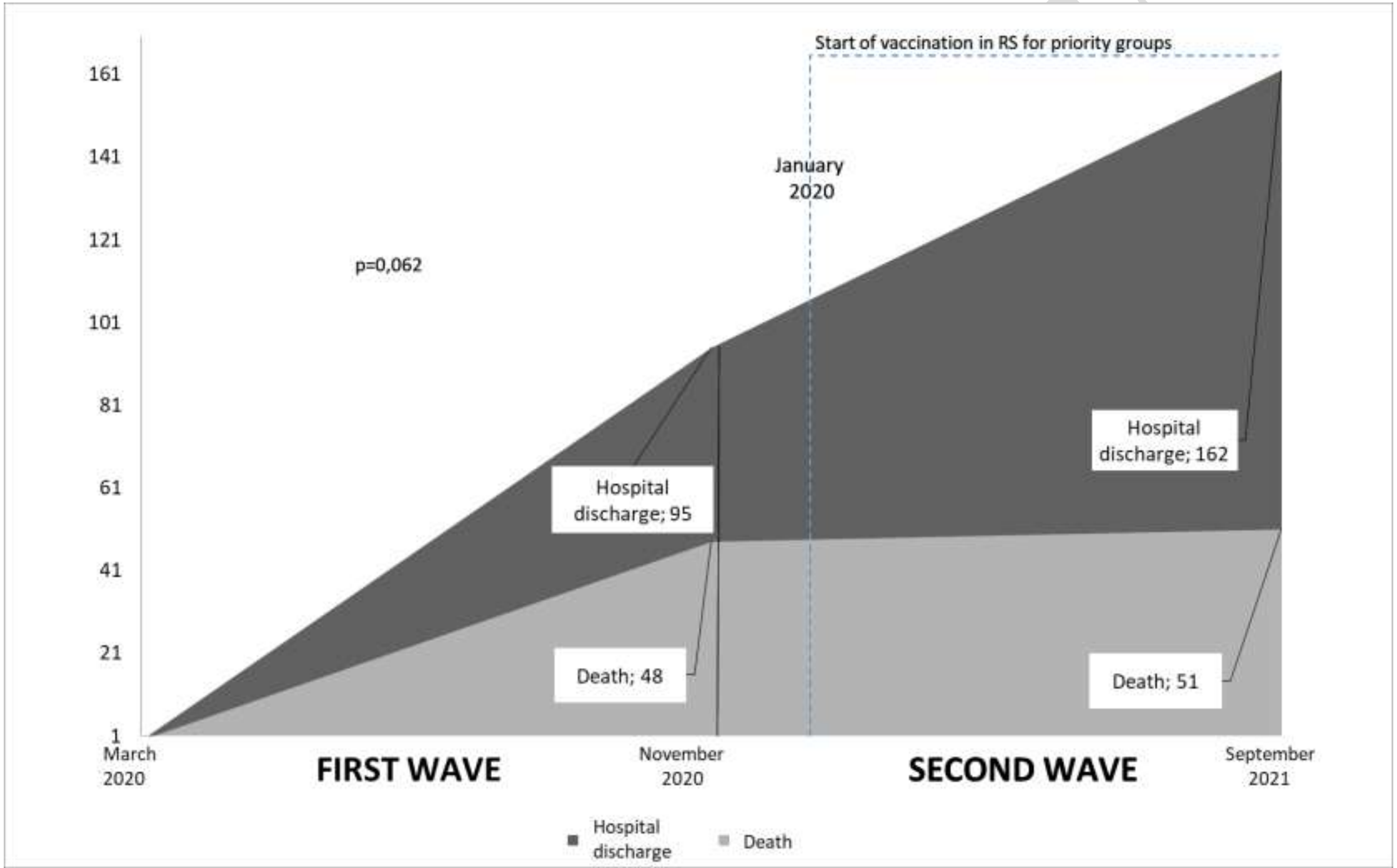
It was identified that the oldest patients were those who died (69 years; IQR 59-76; p<0.001), with longer hospital stays (17.9 days, IQR 10.5-30.1; p=0.005), longer time in intensive care (16.0 days; IQR 6-28.5; p=0.001), more comorbidities (3; IQR 2-4; p=0.037) and overweight (28.4, IQR 24.7-31.2; p<0.001), when compared with patients who were discharged (Table 1). Regarding laboratory tests, patients who died had lower eGFR (43.5, IQR 21.6-43.5; p<0.001), elevated D-dimer (2.1, IQR 1.0-8.3; p<0.001), CRP (145.7, IQR 95.2-259.2; p<0.001), urea (75.0, IQR 44.0-123.0; p<0.001), and INR (1.1, IQR 1.0-1.3; p<0.001) compared to survivors.

Among the sociodemographic characteristics, 33.9% (n=59) of the patients with elementary education and all (n=6; 100%) of the institutionalized patients died (Table 2). Regarding their origin, 79.0% (n=162) of the patients who were admitted by spontaneous demand were discharged, while 36.4% (n=52) of the patients brought by the Mobile Emergency Care Service (MECS) or transferred from another hospital died (p<0.05). Thirty patients (37.5%) who had already been treated at another hospital died. Most patients (n=155, 43.7%) had previously sought the emergency department of the hospital.

Patients admitted in poor general condition (n=11; 68.6%; p<0.001), malnourished (BMI less than 18.49) (n=11; 55.0%; p=0.030), without a previous diagnosis of COVID-19 (n=57; 33.5%; p=0.029), with symptoms other than flu-like or respiratory (n=30; 44.8%; p=0.001), with two or more comorbidities (n=72; 31.9%; p<0.001), with moderate to severe renal function impairment and renal failure (n=49; 53.3%; p<0.001), with polypharmacy (n=24; 63.2%; p=0.033) and who were already hospitalized on mechanical ventilation (n=27; 62.8%; p<0.001) had a higher frequency of death than the others (Table 2).

Regarding complications during hospitalization, the patients with higher mortality rates were those who needed an intensive care bed (34.3%; 85; p<0.001), for a time equal to or greater than 8 days (42.6%; 63; p=0.001) and mechanical ventilation (46.7%; 78; p<0.001). In addition, those who had PTE (24; 42.1%, p=0.014), AKI (55; 53.9%; p<0.001), and VAP (36; 47.4%, p<0.001) and who needed to undergo thoracostomy (9; 75%, p=0.001), tracheostomy (14; 48.3%; p=0.019), and dialysis (48; 69.6%; p<0.001) had a higher frequency of death. No differences were found between the period of the pandemic (wave) and the mortality outcome (p=0.062) (Figure 2). Patients hospitalized in the first wave were older (65.0 years; IQR 54.0–73.0; p<0.001), remained hospitalized for more days (13.7 days; 7.5–28.7; IQR 0.005), spent more days in intensive care (16.5 days, IQR 7.0 – 28.0), were overweight (28.8; IQR 25.8–32.4; $p<0.001$), had a higher number of comorbidities (3; IQR 2-4; $p=0.005$), had a history of smoking ($p=0.009$), and had a greater need for dialysis ($p=0.001$) compared to patients hospitalized in the second wave.

Figure 2 – Absolute and temporal distribution of the outcome of death and discharge among patients hospitalized with COVID-19 for a time equal to or greater than 48 hours at the Hospital de Clínicas de Porto Alegre during the first and second waves of COVID-19 in Rio Grande do Sul (n=356).



The most frequent chronic diseases were hypertensive (n=195; 54.8%), endocrine disorders (n=140; 39.3%), circulatory diseases (n=59; 16.6%), and respiratory diseases (n=54; 15.2%). There were no differences between chronic diseases versus outcome and period of the pandemic. Among the main causes of death, in descending order, were coronavirus infection of unspecified location (n=41; 41.41%), unspecified septicemia (n=16; 16.16%), and severe acute respiratory syndrome (n=14; 14.14%).

Several risk factors were related to the outcome of death in Poisson regression. Among the factors that showed the highest prevalence in the bivariate analysis, in descending order, were: prolonged mechanical ventilation (>21 days) (PR 4.68; CI 95% 3.02 – 7.25), need for dialysis (PR 3.90; CI 95% 2.90-5.93), elevated INR at admission (PR 3.83; CI 95% 2.41-6.07), institutionalization (PR 3.76; CI 95% 3.16–4.47), time longer than seven days in intensive care (PR 3.28; CI 95% 1.94-5.54), and presence of ARI (PR 3.10; CI 95% 2.24-4.28) (Table 3). After multivariate analysis, institutionalized patients (PR 8.81; CI 95% 3.61-21.52), patients on prolonged mechanical ventilation (>21 days) (PR 6.60; CI 95% 3.33-13.05), those on mechanical ventilation for up to 21 days (PR 4.53; CI 95% 2.15-9.50), elevated INR at admission (PR 1.63; CI 95% 1.14 – 2.35), age over 65 years (PR 1.71; CI 95% 1.26-2.36), requiring dialysis (PR 1.44; CI 95% 1.04 – 2.01), and AKI (PR 1.44; CI 95% 1.02 – 2.21) had a higher prevalence of death.

Table 3 – Bivariate and multivariate Poisson multiple analysis regression for factors related to the outcome of death among patients hospitalized for 48 hours or more due to COVID-19.

	Bivariate analysis			Multivariate analysis (n=321)		
	PR	**CI 95%**	***p***	***PR***	**CI 95%**	***p***
Age over 65 years (n=356)	2,34	1,66 – 3,30	<0,001*	1,71	1,26 - 2,36	0,001*
Being institutionalized (n=356)	3,76	3,16 – 4,47	<0,001*	8,81	3,61 – 21,52	0,001*
More than seven days in intensive care (n=356)[1]	3,28	1,94 – 5,54	<0,001*	-	-	-
One to seven days in intensive care (n=356)[1]	1,69	0,92 – 3,13	0,090	-	-	-
Two or more comorbidities (n=356)	2,31	1,18 - 4,51	0,014*	1,52	0,80 – 2,89	0,197
One comorbidity (n=356)	1,91	0,904 – 4,05	0,090	-	-	-
PTE (n=355)	1,67	1,16 – 2,40	0,005*	1,29	0,95 – 1,76	0,099
ARF (n=355)	3,10	2,24 – 4,28	<0,001*	1,44	1,02 – 2,04	0,034*
Admission to mechanical ventilation (n=356)	2,81	2,00 – 3,94	<0,001*	0,76	0,51 – 1,12	0,177
Admission with oxygen therapy, NIV, HFNC or tracheostomy (n=356)	1,10	0,72 – 1,69	0,637	-	-	-
Need for mechanical ventilation during hospitalization (n=356)[1]	3,46	2,44 – 4,91	<0,001*	-	-	-
Prolonged mechanical ventilation (>21 dias) (n=356)	4,68	3,02 – 7,25	<0,001*	6,60	3,33 – 13,05	<0,001*
Mechanical ventilation for up to 21 days (n=356)	2,86	1,58 – 5,17	<0,001*	4,53	2,15 – 9,50	<0,001*
Need for dialysis (n=355)	3,90	2,90 – 5,23	<0,001*	1,44	1,04 – 2,01	0,028*
Polypharmacy (n=356)	1,28	0,90 – 1,81	0,165	-	-	-
D-Dimer (n=332)	1,04	1,02 – 1,06	<0,001*	1,11	0,99 - 1,26	0,062
C-RP (n=352)	1,25	0,94 – 1,67	0,119	-	-	-
Urea (n=356)	2,49	2,07 – 3,00	<0,001*	1,33	0,98 – 1,80	0,065
INR (n=341)	3,83	2,41 – 6,07	<0,001*	1,63	1,14 - 2,35	0,007*

PTE: pulmonary thromboembolism. ARF: acute respiratory failure. NIV: non-invasive ventilation. HFNC: high-flow nasal cannula. C-RP: C-reative protein. INR: International Standard Ratio. PR: prevalence ratio. CI: confidence interval. Statistical significance considered $p \leq 0.050$.[1] Excluded in multivariate analysis due to multicollinearity.

DISCUSSION

Brazilian studies carried out between the initial and most intense period of the pandemic, found variations in the mortality rates of patients hospitalized for COVID-19, ranging from 56% in Mato Grosso do Sul between February 2020 and September 2021, 37.9% in Rio de Janeiro between March and July 2020, to 25.9% in Piauí between March 2020 and March 2021[18–20], and these differences are possibly related to sociodemographic differences and access to health care among the regions of Brazil. In our study, 27.8% (n=99) of the participants hospitalized for 48 hours or more died. It should be noted that the research period comprised three semesters covering the two waves of COVID-19 in Brazil and that, only in the last semester, the distribution of the vaccine in Brazil had begun.

Among the variables related to mortality, our findings corroborate national and international studies that consider advanced age as a risk factor for death[7,18–25]. The higher mortality rate of patients with low levels of education was also observed in two Brazilian studies by Sansone[25] and Silva[26], reducing as the level of education increases. This is partly because education is strongly related to greater access to health. The lower educational level and, consequently, the lower income, result in more precarious housing conditions, making it difficult to maintain social isolation and impacting access to health care as well as the transmission, diagnosis, and treatment of COVID-19, all exacerbated by the lack of financial conditions for the acquisition of personal protective equipment as well as hand and environmental hygiene[6,26–29].

There was no association between smoking history and death, which has also been reported by other authors[23,24,30]. Recently, a systematic review by Baker[31] investigated the impact of tobacco use on COVID-19 outcomes. Of the 28 studies that assessed mortality, 12 found no significant association, 15 found an increased risk of death, and one found a decreased risk of death. In view of this, and as the harm of cigarette use is widely established and proven in our society, it is possible that the habit was not reported by the participants, with an under-identification of the cases.

The presence of comorbidities has been reported to be associated with a higher chance of death in several studies[18,19,22,23,26]. This finding corroborates our study, in which we identified that patients whose outcome was death had a higher number of comorbidities than those who were discharged, in addition to the fact that 86.2% (n=50) of patients who did not have any comorbidities had a favorable outcome, while patients with two or more comorbidities (n=72; 31.9%) had a higher frequency of death. Among the comorbidities, the presence of cerebrovascular diseases, heart problems, hypertension[23], and diabetes[24] are factors associated with higher lethality. In our study, we did not identify a significant relationship between the outcome, pandemic period, and previous chronic diseases. Many of the comorbidities associated with in-hospital death due to COVID-19 are also associated with the death of non-COVID-19 patients, suggesting that the disease primarily amplifies the pre-existing risks faced by patients with these diseases[32].

The death of all patients who were institutionalized may be related to their fragile health, the quality of health care in LTCFs in the face of an unknown disease, and the delay in referral to hospital care, with the subsequent worsening of their health condition. No other studies were found that analyzed this social condition. However, a study by Machado[33] estimated that 44.7% of deaths from COVID-19 would occur among institutionalized older adults.

Although some studies have considered obesity as a risk factor for death from COVID-19[24,34,35], our study found no relationship with this nutritional status. International studies with patients hospitalized for COVID-19, such as the prospective cohort conducted in two hospitals in New York by Cummings[36], found no evidence that obesity is a risk factor for hospital death in patients with COVID-19, and the study by Bedock[37] did not identify an association between malnutrition and death in patients hospitalized with coronavirus in a university hospital in France. Conversely, we observed that patients with malnutrition had a higher frequency of death; however, the sample size of patients with this condition included in our study was limited, which may have influenced this result.

The behavior of seeking health can vary according to several factors and late presentation to the hospital can be an important determinant of hospital outcome[9]. This fact can be compared to the results found in our study regarding the history of contagion, where patients who had already had a previous diagnosis of COVID-19 presented favorable results compared to those who had not yet been diagnosed with the infection. A scoping review by Pujolar[38] identified that fear of contagion was one of the main reasons for the population not going to health services. Another qualitative study developed in Rio de Janeiro showed that the first signs and symptoms of COVID-19, as well as their persistence, determined the search for medical care in health services, which was the beginning of the therapeutic itinerary. Among the difficulties reported were the lack of access to diagnostic testing and the need to navigate among various health services are mentioned[39]. Within this context, in Brazil, the initial orientation established by the Ministry of Health was to manage mild cases with non-therapeutic measures, medications for symptomatic relief, and home isolation and, only in the presence of signs of severity, refer the patient to the Reference Center for COVID-19 in the region[3]. Considering that our study was developed in a high-complexity public hospital, most patients had already sought care in other health services initially, and the emergency service was identified as the one with the highest demand.

It should be noted that the process of regulating hospital beds in the state has undergone changes throughout the phases of the pandemic[5]. Through the State Hospital Contingency Plan, the guidelines for the organization of hospitals were established. At first, in phases 1 and 2, the Plan listed the HCPA, along with another reference hospital in Porto Alegre, as the front line of care for patients with COVID-19. In phase 3, hospitals in the health macro-regions started to offer medium complexity and back-up beds due to the increase in demand for high complexity. In phase 4, care was initiated in field hospitals and emergency care units, and a state of hospital emergency was declared in RS, due to insufficient bed availability and exhaustion of resources in the state.

Regarding symptoms and history of contagion, 77.4% (n=144) of the patients who had already been diagnosed with COVID-19 at the time of admission were discharged. This finding demonstrates that timely diagnosis allows the search for health care in a more appropriate and efficient way, while 33.5% (n=57) of the patients who were diagnosed after hospitalization died, indicating the worsening of the condition with late confirmation of the disease. In addition, 44.8% of patients who had nonspecific (non-flu-like) symptoms died. This fact may be related to the longer time for diagnosis of the disease at the beginning of the pandemic and the emergence of variants in Brazil that led to a variability of symptoms and intensity, making it difficult to associate these with possible contamination. Flu-like symptoms and dyspnea continue to be the most frequently found, similar to those found by Marcolino[40] and Zeiser[6], however, without significant differences in terms of outcome.

The relationship between polypharmacy and COVID-19 has been described by several authors[41–43]. In our study, polypharmacy was present in 22.8% (n=38) of the patients, a rate lower than the findings of the systematic review and meta-analysis conducted by Ghasemi[43], in which the overall prevalence of polypharmacy in patients with COVID-19 was 34.6%. Systematic review of Iloanusi, Mgbere, and Essien[41] identified associations between polypharmacy and death in patients with COVID-19 in five of seven studies; however, in our study, after regression analysis, polypharmacy was not associated as a potential risk factor for death (p=0.165).

Regarding laboratory data, elevated D-dimer, CRP, urea, and INR results in patients with unfavorable prognosis are in agreement with other studies, which have reported an increased risk of disease progression and death[21,23,44]. A study conducted with patients hospitalized with COVID-19 in the USA by Berger[45] found that individuals with elevated D-dimer were more likely to become seriously ill and require invasive mechanical ventilation, in addition to having a higher proportion of thrombotic events and acute kidney injury.

The need for hospitalization in an intensive care bed and invasive ventilatory support are widely discussed in the literature as factors indicative of severe condition and are related to a higher chance of death[23,25,26]. A systematic review and meta-analysis by Ippolito[46] identified that one in two patients with COVID-19 may develop VAP during ICU stay. In our study, 21.4% (n=76) of the patients had VAP and, of these, 47.4% (n=36; $p<0.001$) died. Prolonged periods of mechanical ventilation, prone positioning, and use of immunomodulatory therapies, which are very common in patients with COVID-19, may have increased the risk of developing VAP. In addition, the scenario of overcrowded ICUs in the peak period of the pandemic, limited human resources, and more episodes of cross-contamination are factors that may have contributed to this high rate[46].

Severe acute kidney injury, which in our study was associated with a higher chance of death, leading to the need for renal replacement therapy (RRT) during hospitalization, is the complication most frequently reported by several authors[23,24,36,44,47]. Cummings[36], in his prospective cohort study in the USA, estimates that 31% of hospitalized patients developed severe acute kidney injury requiring RRT, which had considerable implications for the allocation of resources, given the limited supplies of equipment and consumable materials, together with the need for qualified personnel to meet the demand.

As already described by Zeiser, the prognosis of COVID-19 is related to the waiting time for hospital and ICU admission, where the percentage of deaths increases at all ages when the number of days until hospitalization and intensive care increases[6]. The regional differences observed in our study, compared to other regions of Brazil and the world, may be related to social and health inequalities, local social distancing and prevention strategies, quality and availability of health services, medical supplies and resources, prevalence of different SARS-CoV-2 variants, treatment strategies, as well as the availability of qualified human resources in sufficient numbers to meet demand.

In RS, vaccination against COVID-19 began to be distributed to specific groups of the population in early 2021. For this reason, a small number of patients included in our study had received the vaccine, and it was not possible to assess mortality among vaccinated and unvaccinated patients.

This study has some important limitations. Due to the retrospective observational nature, some data were not recorded in the computerized medical records and could not be retrieved. Additionally, important information may not have been described or may have been reported incompletely in the evolution of the professionals, leading to divergence in the data collected and, consequently, in their interpretation and statistical strength. For this reason, we chose to exclude patients who died in less than 24 hours and with a hospital stay of less than 48 hours due to the higher proportion of incomplete data for the variables of interest in these patients. Variables for which data could not be collected or for which a large proportion of patients did not have the information in the electronic medical record were also excluded from the analysis.

As this is a single, university-based, high-complexity study, it is inferred that there is greater severity in the health status of the patients, which may have influenced the unfavorable outcomes and, therefore, the results may be overestimated. It is noteworthy that the cross-sectional nature of the study does not allow the identification of patients who required readmission or who died after hospital discharge, and this limitation may also characterize a bias in the results.

One of the main strengths of the study is the fact that it is based on a database of real cases. The data were obtained through an extensive review of medical records, resulting in a greater degree of detail than the electronic extraction of structured data elements. Although it was carried out in a high-complexity public hospital in Rio Grande do Sul, the data presented can be extrapolated to other Brazilian public hospitals that operate within the same context. The data underwent periodic auditing to ensure quality, and the analysis provided a thorough assessment of various outcomes in hospitalized COVID-19 patients.

CONCLUSION

Differences were found between the clinical-epidemiological characteristics and mortality of patients who were admitted to a high-complexity university hospital in RS for a time equal to or greater than 48 hours during the two waves of the COVID-19 pandemic. In the first wave, a higher frequency of patients over 65 years of age, longer hospital stays, more days in intensive care, overweight, a higher number of comorbidities, history of smoking, and need for dialysis were identified when compared to patients infected in the second wave of the pandemic in RS. After multivariate analysis, the factors related to death were institutionalization, prolonged mechanical ventilation for less than 21 days, high INR at admission, age over 65 years, need for dialysis, and presence of ARI. The findings of this study can help in the knowledge of the behavior of COVID-19 in RS, in the improvement of patients' health outcomes, and can provide subsidies for the training and allocation of workforce and supplies in scenarios of resource scarcity and exponential demands for care, such as disease outbreaks and epidemics.

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