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ORIGINAL ARTICLE

Factors associated with mortality in critically ill patients with COVID-19

Fatores associados à mortalidade em pacientes críticos com COVID-19

Factores asociados a la mortalidad en pacientes críticos con COVID-19

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ABSTRACT

Background and objectives: COVID-19 is a life-threatening disease. Recognizing the main characteristics of the disease and its main complications will help future interventions, care, and management of health services since territorial and population diversities directly influence health outcomes. Our main objective is to describe the clinical characteristics, outcomes, and factors associated with mortality of patients with COVID-19 admitted to the intensive care unit of a public and tertiary hospital. **Methods:** Cohort study, conducted from March 1 to September 30, 2020. Poisson regression was performed to investigate the variables of hospital treatment as potential risk factors for in-hospital mortality. **Results:** Of the 283 eligible patients in this study, the hospital mortality rate was of 41.7% (n=118). The most common outcomes were acute respiratory distress syndrome, nosocomial infection, and septic shock. Factors independently associated with increased risk of death were age greater than 51 years old (RR=1.7, 95%CI=1.0-2.8), especially over 70 years old (RR=2.9, 95%CI=1.7-2.8), current smoker (RR=1.8, 95%CI=1.1-2.9), requiring the use of inotrope (RR=1.4, 95%CI=1.0-2.0), and presenting potassium greater than 5.0 mEq/l on admission (RR=1.3, 95%CI=1.0-1.7). **Conclusion:** Mortality was associated with older age, being a current smoker, inotrope use, and presenting potassium greater than 5.0 on hospital admission.

Keywords*: COVID-19. Intensive Care Units. Epidemiological Profile. Morbidity. Hospital Mortality.*

RESUMO

Justificativa e objetivos: A COVID-19 é uma doença ameaçadora à vida. Reconhecer as características da doença e suas principais complicações nesta população auxiliará em futuras intervenções, cuidados e gestão dos serviços de saúde, uma vez que a diversidade territorial e populacional influencia diretamente nos resultados de saúde. O objetivo principal do presente estudo é descrever as características clínicas, desfechos e fatores associados à mortalidade de pacientes com COVID-19 internados na unidade de terapia intensiva de um hospital público e

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terciário. **Métodos:** Estudo de coorte, realizado de 1º de março a 30 de setembro de 2020. Foi realizada regressão de Poisson para investigar variáveis de apresentação hospitalar como potenciais fatores de risco para mortalidade intra-hospitalar. **Resultados:** Dos 283 pacientes elegíveis neste estudo, o dado de mortalidade hospitalar foi de 41,7% (n=118). Os desfechos mais comuns foram síndrome do desconforto respiratório agudo, infecção hospitalar e choque séptico. Os fatores independentemente associados ao aumento do risco de morte foram idade superior a 51 anos (RR=1,7, IC 95%=1,0-2,8), principalmente acima de 70 anos (RR=2,9, IC 95%=1,7-2,8), tabagismo atual (RR=1,8, IC 95%=1,1-2,9), necessidade de inotrópico (RR=1,4, IC 95%=1,0-2,0) e potássio maior que 5,0 mEq/l (RR=1,3, IC 95%=1,0-1.7) na admissão. Conclusão: A mortalidade esteve associada à idade avançada, tabagismo atual, uso de inotrópicos e potássio maior que 5,0 na admissão hospitalar.

***Descritores**: COVID-19. Unidades de Terapia Intensiva. Perfil Epidemiológico. Morbidade. Mortalidade Hospitalar.*

RESUMEN

Justificación y objetivos: La COVID-19 es una enfermedad potencialmente mortal. Reconocer las características de la enfermedad y sus principales complicaciones en esta población ayudará a futuras intervenciones, atención y gestión de los servicios de salud, ya que las diversidades territoriales y poblacionales influyen directamente en los resultados de salud. El objetivo principal de este estudio es describir las características clínicas, los resultados y los factores asociados a la mortalidad de los pacientes con COVID-19 ingresados en la unidad de cuidados intensivos de un hospital público y de tercer nivel. **Métodos**: Estudio de cohorte, realizado del 1 de marzo al 30 de septiembre de 2020. Se realizó regresión de Poisson para investigar variables en la presentación hospitalaria como potenciales factores de riesgo para la mortalidad intrahospitalaria. **Resultados:** De los 283 pacientes elegibles en este estudio, el 41,7% (n=118) tuvo mortalidad hospitalaria. Los desenlaces más comunes fueron síndrome de dificultad respiratoria aguda, infección nosocomial y shock séptico. Los factores independientemente asociados a mayor riesgo de muerte fueron edad mayor de 51 años (RR=1,7, IC95%=1,0-2,8), especialmente mayores de 70 años (RR=2,9, IC95%=1,7-2,8), tabaquismo actual (RR=1,8, IC95%=1,1-2,9), necesidad de inotrópico (RR=1,4, IC95%=1,0-2,0) y potasio mayor que 5,0 mEq/l (RR=1,3, IC95%=1,0-1,7). **Conclusión:** La mortalidad estuvo asociada a la edad avanzada, tabaquismo actual, uso de inotrópico y potasio mayor a 5,0 en la admisión hospitalaria.

***Palabras clave:** COVID-19. Unidades de Cuidados Intensivos. Perfil Epidemiológico. Morbilidad. Mortalidad Hospitalaria.*

INTRODUCTION

Coronavirus is a significant human and animal pathogen. In late 2019, a new coronavirus was identified as the cause of a set of pneumonia cases in Wuhan, a city in Hubei Province, China. Its rapid dissemination led to an epidemic in that country, followed by increasing number of cases in other countries.[1] The World Health Organization (WHO) designated, in February 2020, the name 'coronavirus disease 2019' (COVID-19) to the emerging disease; elevating the worldwide outbreak to a pandemic status, on March 11 of the same year.[2]

The most common symptoms of COVID-19 are fever, dry cough, and tiredness. Most people (about 80%) recover from this disease without hospital treatment. More than 80% of the cases have mild to moderate symptoms, approximately 15% have severe illness requiring hospitalization, and around 5% require intensive care support.[3] Critical patients with COVID-19 who are admitted to the Intensive Care Unit (ICU) required multi-organ support and long-term care.[4]

The infection caused by this new coronavirus (the SARS-CoV-2) has caused an extreme health problem; many patients have progressed to severe respiratory illness or other complications within a short period of time. The pandemic affected the world, leading several healthcare systems to collapse.

COVID-19 is a life-threatening disease. Studies worldwide have described the clinical and epidemiological characteristics, risk factors, case management, and symptoms associated with patients infected with COVID-19. However, recognizing the characteristics of the disease and its main complications in the local population helps future interventions, care, and management of health services in this region, since territorial and population diversities directly influence health outcomes. The main objective of this study is to describe the clinical characteristics, outcomes, and factors associated to mortality of patients with COVID-19 admitted to the intensive care unit of a public and tertiary hospital.

METHODS

Observational study, based on a cohort of records of patients with COVID-19 admitted to the ICU of the Hospital Nossa Senhora da Conceição (HNSC). This study is part of a multicentered research project entitled "*Avaliação do perfil laboratorial, radiológico e sintomatológico de pacientes infectados com o novo coronavírus 2019 (SARVS-CoV-2) em hospitais brasileiros*" (Evaluation of the laboratory, radiological and symptomatological profile of patients infected with the new coronavirus 2019 (SARS-CoV-2) in Brazilian hospitals) conducted by

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the Federal University of Minas Gerais (UFMG), in which the Grupo Hospitalar Conceição (GHC) is a participating center.

The GHC is a reference within the service of the Brazilian Unified Health System (SUS), associated to the Ministry of Health, this nationally recognized structure forms the largest public network of hospitals in the South of the country, with 100% SUS service.[5]

The work was approved by the Research Ethics Committee of Grupo Hospitalar Conceição on June 24, 2020, under opinion 4,108,686 on Plataforma Brasil.

Participants and collection period

Records of patients admitted to the ICU of the HNSC with confirmed diagnosis of COVID-19 from RT-PCR or IgM in serological test (conventional serology or rapid test), in the period from March 1 to September 30, 2020, were eligible. Patients who were admitted to the hospital for other causes and developed COVID-19 during their hospital stay and patients who were diagnosed with COVID-19 by antigen test were excluded. No sampling was performed.

Data collection took place from July 2020 to January 2021, by a group of eight previously trained nurses, including the main researcher, belonging to the Research Group of the Multicenter Project.

The records of eligible patients were selected sequentially by the date of admission, and data were collected at three different times (admission, hospital stay, and discharge or death). The following variables were collected: demographic characteristics, past medical history, clinical manifestations at admission, additional tests at admission (first tests recorded, within 24 hours of admission), supportive care, and health outcomes. In cases of transfer to another hospital, an active search for patient outcomes was performed at the institution to which the patient was transferred.

Data collection was conducted via Research Electronic Data Capture (REDcap), a platform for collecting, managing, and disseminating research data. The data were periodically audited.

Statistical analysis

Descriptive analyzes were used to present all variables. The Shapiro-Wilk normality test was performed to verify the normal distribution of continuous variables. Variables that were abnormally distributed were described using medians and interquartile ranges (IQR). Categorical variables were presented in absolute numbers and percentages.

Poisson regression with robust variance estimation (relative risk [RR], 95% confidence interval [95%CI]) was used to investigate variables at hospital presentation as potential risk factors for in-hospital mortality. For the multivariate model, age and variables with $p<0.05$ in the univariate analysis were included.

Statistical analyzes were conducted using IBM SPSS Statistics (IBM SPSS Statistics for Macintosh, version 20.0. Armonk, NY: IBM Corp.).

RESULTS

A total of 400 patients were hospitalized in the COVID ICU of the HNSC for suspected disease from March 1 to September 30, 2020. Of these, 75 had negative tests and the other 325 had confirmed SARS-CoV-2 infection. Among those confirmed, 283 were eligible for the study. Among the remaining, 29 were hospitalized for another reason and contracted the virus during hospitalization, and 13 were diagnosed by the antigen test, which was not an inclusion criterion at that time, since the test was still little-known. Of the 283 eligible patients, COVID-19 was confirmed by RT-PCR in 96.8%.

The hospital mortality rate of these patients was 41.7% (n=118). Mortality was 7.9% (n=15) in those younger than 50 years, 37.5% (n=48) between 51 and 70 years, and 74.3% (n=55) in those over 70 years. The median time between admission and death was 17 days (IQR: 11 – 27.2).

The median time from symptom onset to admission was 5 days (IQR=2 – 7), and to ICU admission was 7 days (IQR=4 – 10). The median length of hospital stay was 20 days (IQI=13 – 32) and the median length of stay in the ICU was 12 days (IQR: 7 – 22).

Men represented 52.6% of the study population (Table 1), and the mean age of patients was 59.1 years (SD=15).

Overall, 27.2% (n=77) of patients had one comorbidity, 29.6% (n=84) had two comorbidities, and 21.2% (n=60) had three or more comorbidities. The death rate for one, two, and three comorbidities or more was 20.3% (n=24), 38.1% (n=45), and 24.5% (n=29) respectively.

Systemic arterial hypertension (SAH) (54.7%), diabetes mellitus (DM) (35.6%), and obesity (23.3%) were the most frequent comorbidities. Patients who died were more likely to have cardiovascular disease and DM. Patients with hematological diseases had death outcomes in 77.8% of cases (nine patients with hematological disease, seven died).

Among the lifestyle habits investigated, those who were former smokers was the most frequent, 22.6% (n=64). Of these, 56.3% died (n=36, RR=1.5, 95%CI=1.1 – 2.1). Dyspnea (68.9%), fever (55.8%), and dry cough (46.2%) were the most common symptoms among all patients and the most frequent among patients who died (Table 2).

At hospital admission, respiratory rate >30 bpm was found in 19.4% (n=46) of the sample, 44.3% (n=122) of patients had oxygen saturation <92% on arrival, 23.3 % (n=49) had fever (higher temperature >37.8°C), and 33.7% (86) had tachycardia (HR>100 bpm). 55.4% of the patients used supplemental oxygen, and 14.8% of these required IMV (n=42, RR=1.7, 95%CI=1.2 – 2.4). Inotropes were required in 10.6% (n=30, RR=1.8, 95%CI=1.3 – 2.4) of the cases.

Lymphopenia (<1000/uL) was found in 54.9% (n=155) of 282 patients, elevated D-dimer (>500 ng/mL) was found in 81.4% (n=198) of 243 patients, elevated C-reactive protein (>100 mg/L) was found in 61.1% (n=151) of 247 patients, elevated serum creatinine (>1.2 mg/dl) in 30.6% (n=86) of 281 patients (Table 3). Laboratory tests were not requested for all patients.

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Table 1. Demographics, comorbidities, and life habits of patients admitted to the HNSC Adult COVID ICU from March 1 to September 30, 2020.

Characteristic	Discharged alive N (%) (n=165)	Died N (%) (n=118)	Total N (%) (n= 283)	*p value*
Age <50 years	66 (40.0)	15 (7.9)	81 (28.6)	**<0.001**
Age 51 to 70 years	80 (48.4)	48 (40.6)	128 (45.2)	**<0.001**
Age >70 years	19 (11.5)	55 (46.6)	74 (26.1)	**<0.001**
Male	89 (53.9)	60 (50.8)	149 (52.6)	0.607
Female	76 (46.0)	58 (49.1)	134 (47.3)	0.607
Healthcare professional	10 (6.0)	2 (1.6)	12 (4.2)	0.146
Comorbidity				
Hypertension	85 (51.5)	70 (59.3)	155 (54.7)	0.198
Coronary artery disease	12 (7.2)	11 (9.3)	23 (8.1)	0.514
Heart failure	5 (3.0)	14 (11.8)	19 (6.7)	**<0.001**
Atrial fibrillation/flutter	3 (1.8)	5 (4.2)	8 (2.8)	0.139
Ischemic stroke	5 (3.0)	14 (11.8)	19 (6.7)	**<0.001**
Asthma	21 (12.7)	7 (5.9)	28 (9.8)	0.098
COPD	14 (8.4)	15 (12.7)	29 (10.2)	0.212
Diabetes mellitus	53 (32.1)	48 (40.6)	101 (35.6)	0.132
Obesity	47 (28.4)	19 (16.1)	66 (23.3)	**0.026**
Cancer	10 (6.0)	16 (13.5)	26 (9.1)	**0.011**
Hematology	2 (1.2)	7 (5.9)	9 (3.1)	**0.001**
Solid organ	8 (4.8)	9 (7.6)	17 (6.0)	0.286
Chronic kidney disease	7 (4.2)	8 (6.7)	15 (5.3)	0.299
Lifestyle habits				
Illicit drugs	4 (2.4)	3 (2.5)	7 (2.4)	0.949
Alcoholism	6 (3.6)	4 (3.3)	10 (3.5)	0.913
Former smoker	28 (16.9)	36 (30.5)	64 (22.6)	**0.002**
Current smoker	10 (6.0)	12 (10.1)	22 (7.7)	**0.048**
Total	165 (100)	118 (100)	283 (100)	-

COPD: chronic obstructive pulmonary disease.

Table 2. Symptoms, clinical data, and oxygen requirement at admission of patients to the HNSC Adult COVID ICU, from March 1 to September 30, 2020.

Symptom and clinical data	Discharged alive N (%) (n=165)	Died N (%) (n=118)	Total N (%) (n= 283)	*p value*
Adynamia	43 (26.0)	26 (22.0)	69 (24.3)	0.448
Ageusia	11 (6.6)	2 (1.6)	13 (4.5)	0.116
Anosmia	12 (7.2)	1 (0.8)	13 (4.5)	0.073
Headache	32 (19.3)	10 (8.4)	42 (14.8)	**0.027**
Diarrhea	16 (9.6)	12 (10.1)	28 (9.8)	0.895
Dyspnea	110 (66.6)	85 (72.0)	195 (68.9)	0.347
Fever	103 (62.4)	55 (46.6)	158 (55.8)	**0.008**
Myalgia	63 (38.1)	21 (17.7)	84 (29.6)	**0.001**
Nausea / vomiting	13 (7.8)	10 (8.4)	23 (8.1)	0.854
Productive cough	16 (9.6)	16 (13.5)	32 (11.3)	0.282
Dry cough	83 (50.3)	48 (40.6)	131 (46.2)	0.114
Inotrope use	9 (5.4)	21 (17.7)	30 (10.6)	**<0.001**
SBP <90 mmHg e DBP <60	(n=145) 3 (2.0)	(n=104) 3 (2.8)	(n=249) 6 (2.4)	0.656
HR >100 bpm	(n=147) 51 (34.6)	(n=108) 35 (32.4)	(n=255) 86 (33.7)	**0.009**
RR >30 mrpm	(n=141) 31 (21.9)	(n=95) 15 (15.7)	(n=236) 46 (19.4)	0.263
Fever >37.8°C	(n=125) 31 (24.8)	(n=82) 18 (21.9)	(n=207) 49 (23.6)	0.643
Peripheral oxygen saturation <92	(n=160) 73 (45.6)	(n=115) 49 (42.6)	(n=275) 122 (44.3)	0.621
Oxygen -1-6L/min	46 (27.8)	36 (30.5)	82 (28.9)	0.189
Oxygen - >7L/min	23 (13.9)	10 (8.4)	33 (11.6)	0.627
Invasive mechanical ventilation	17 (10.3)	25 (21.1)	42 (14.8)	**0.002**

HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate.

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Table 3. Laboratory parameters at admission of patients admitted to the adult COVID ICU of the HNSC, from March 1 to September 30, 2020.

Laboratory Parameter	Discharged alive N (%)	Died N (%)	Total N (%)	*p value*
Hemoglobin (g/dL)	**(n=164)** 61 (37.1)	**(n=118)** 54 (45.7)	**(n= 282)** < 12.8 (115) (40.7)	0.145
White blood cell (/uL)	42 (25.6)	39 (33.0)	< 3600 (12) (4.2)	**0.011**
			>11000 (81) (28.7)	0.095
Lymphocytes (/uL)	84 (51.2)	71 (60.1)	< 1000 (155) (54.9)	0.141
Platelets (/uL)	**(n=153)** 21 (13.7)	**(n=112)** 26 (23.2)	**(n=265)** <150000 (47) (17.7)	**0.030**
Urea (mg/dL)	**(n=162)** 31 (19.1)	**(n=116)** 54 (46.5)	**(n=278)** >50 (85) (30.5)	**<0.001**
Potassium (mEq/L)	**(n=160)** 14 (8.7)	**(n=116**) 6 (5.1)	**(n=276)** < 3.5 (20) (7.2)	0.507
	15 (9.3)	30 (25.8)	> 5.0 (45) (16.3)	**<0.001**
Sodium (mEq/L)	**(n=157)** 42 (26.7)	**(n=114)** 38 (33.3)	**(n=271)** <135 (80) (29.5)	0.177
	3 (1.9)	5 (4.3)	>145 (8) (2.9)	0.099
Lactate (mmol/L)	**(n=152)** 39 (25.6)	**(n=106)** 45 (42.4)	**(n=258)** >1.6 (84) (32.5)	**0.003**
C-reactive protein (mg/L)	**(n=144)** 87 (60.4)	**(n=103)** 64 (62.1)	**(n=247)** >100 (151) (61.1)	0.785
Arterial pH	**(n=150)** 13 (8.6)	**(n=102)** 18 (17.6)	**(n=252)** <7.35 (31) (12.3)	**0.037**
	43 (28.6)	22 (21.5)	>7.45 (65) (25.7)	0.421
Arterial PCO2 mmHg	40 (26.6)	40 (39.2)	<32 (80) (31.7)	**0.019**
	16 (10.6)	15 (14.7)	>42 (31) (12.3)	0.118
Arterial PO2 (mmHg)	101 (67.3)	79 (77.4)	<83 (180) (71.4)	0.226
Bicarbonate (mmol/L)	57 (38)	43 (42.1)	<22 (100) (39.6)	0.793
D-dimer (ng/ml FEU)	**(n=143)** 113 (79.0)	**(n=97)** 85 (87.6)	**(n=243)** >500 (198) (81.4)	0.068

Table 3. Supportive therapies and patient outcomes admitted to the HNSC Adult COVID ICU, from March 1 to September 30, 2020.

Supportive Thereaphy	Discharged alive N (%) (n=165)	Died N (%) (n=118)	Total N (%) (n= 283)	*p value*
Inotropes	96 (58.1)	111 (94.0)	207 (73.1)	**<0.001**
Prone position	72 (43.6)	60 (50.8)	132 (46.6)	0.230
Noninvasive mechanical ventilation	21 (12.7)	19 (16.1)	40 (14.1)	0.528
Mechanical ventilation	135 (81.8)	115 (97.4)	250 (88.3)	**0.003**
Prolonged mechanical ventilation > 21 dias	37 (22.4)	34 (28.8)	(n=250) 71 (25.0)	0.731
Need for RRT	28 (16.9)	45 (38.1)	73 (25.7)	**<0.001**
Septic shock	32 (19.3)	67 (56.7)	99 (34.9)	**<0.001**
Nosocomial infection	67 (40.6)	48 (40.6)	115 (40.6)	0.990
Thromboembolism				
Deep vein thrombosis	7 (4.2)	5 (4.2)	12 (4.2)	0.998
Pulmonary thromboembolism	16 (9.6)	13 (11.0)	29 (10.2)	0.712
Bleeding	4 (2.4)	8 (6.7)	12 (4.2)	**0.022**
Hyperglycemia	48 (29.0)	29 (24.5)	77 (27.2)	0.411
ARDS	55 (33.3)	64 (54.2)	119 (42.0)	**<0.001**

ARDS: acute respiratory distress syndrome.

Chest radiographs were obtained in 95% (n=269) patients on admission and they were found to be abnormal in 85.2%. The most common patterns were diffuse interstitial infiltrate (31.2%, n=84) and consolidation (31.2%, n=84). Only 14.8% (n=42) of patients had chest computed tomography on admission, and of these, the most frequent finding was bilateral ground-glass opacity, with 57.1% (n=24) patients.

Of the 283 patients admitted to the ICU, 88% (n=250, RR=5.0, 95%CI=1.7 – 15.0) required invasive mechanical ventilation (IMV). The median time on IMV was 13 days (IQR=7-22.5), and 28.4% (n=71) of the patients used prolonged IMV (≥21 days). The prone maneuver was performed in 46.6% (n=132), 25.7% (n=73, RR=1.7, 95%CI= 1.3 – 2.2) were treated with renal replacement therapy (RRT). The studied center does not have extracorporeal membrane oxygenation (ECMO) therapy and 0.3% (n=1) of the population was transferred to another institution for this purpose. Mortality for those who needed IMV was 46% (n=115), for those who needed the prone position it was 45.5% (n=60), for RRT 61.6% (n=45) and ECMO 100% (n=1). Antibiotic therapy was used in 97.8% of patients.

The most common outcomes (Table 4) during hospitalization of critically ill patients were: acute respiratory distress syndrome (ARDS), present in 42% (n=119, RR=1.6, 95% CI= 1.2 – 2.1) with 54.2% mortality (n=64); nosocomial infection, in 40.6% (n=115) with 40.6% mortality (n=48); and septic shock, in 34.9% (n=99, RR = 2.4,

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95% CI= 1.8 -3.1) with a mortality of 56.7% (n=67). Table 4 summarizes supportive therapies and outcomes during hospitalization.

Poisson regression was performed to assess risk factors for mortality from COVID-19 (Table 5). Factors independently associated with higher risk of death were age over 51 years (RR=1.7, 95%CI=1.0-2.8), especially over 70 years (RR=2.9, 95%CI=1, 7-2.8), current smoker (RR=1.8, 95%CI=1.1-2.9), required vasoactive amines (RR=1.4, 95%CI=1.0-2.0), and potassium greater than 5.0 mEq /L on admission (RR=1.3, 95%CI=1.0-1.7).

Table 5. Risk factors for COVID-19 mortality at admission of patients to the HNSC Adult COVID ICU, from March 1 to September 30, 2020, by Poisson regression.

Characteristic	RR (95% IC)	*p value*
Age >70 years	2.9 (1.7 - 4.9)	<0.001
Age >51 - 70 years	1.7 (1.0 - 2.8)	0.030
Current smoker	1.8 (1.1 – 2.9)	0.014
Inotropes	1.4 (1.0 – 2.0)	0.036
Potassium >5.0	1.3 (1.0 – 1.7)	0.042

DISCUSSION

This study presents the clinical, laboratory, and radiological characteristics and outcomes of patients with COVID-19 admitted to one of the largest ICUs in Southern Brazil, from March 1 to September 30, 2020. The hospital mortality rate of patients who required ICU was 41.7%, similar to that found in other studies.[6-7]

Most of those who were admitted to the ICU for COVID-19 were men.[7-9] The average age in this study was 59.1 years, similar to published studies,[7,10] with higher mortality among the older adults.[11] Advanced age is an independent predictor of mortality and suggests that in older adults with COVID-19 this may be associated with impaired immune response caused by aging cells.[12]

Probably, age itself is closely related to the propensity for comorbidities, which contributes to the transition in severity.[9] The absence of difference in mortality between men and women observed by us was also reported by other authors.[10]

This study is a part of a multicenter study, which reported that 79.8% of the patients had at least one comorbidity, and the mortality of those who had at least one comorbidity was higher than those who had none. Notably, the average number of comorbidities was higher among those who died when compared with those who survived.[13] In our study, 27.2% had at least one comorbidity, 29.6% had two comorbidities and 21.2% had three or more comorbidities, and the death rate for one, two, or three comorbidities was 20.3%, 38.1%, and 24.5%, respectively.

Patients with severe conditions had a higher rate of comorbidities and complications than patients with non--severe conditions.[14] Our study did not evaluate patients who did not need an ICU. We observed higher mortality in patients with two comorbidities when compared with those with only one, but this increase in mortality did not occur in patients with three comorbidities. This may be due to the different effects comorbidities have on mortality (three mild comorbidities can have less of an influence in the outcome than two severe ones) or for statistical reasons.

The comorbidities registered in our work were the most common, similar to those found in a Chinese study,[10] and obesity was the third most frequent comorbidity. Angiotensin-converting enzyme is abundantly expressed in adipose tissue, which may make obese individuals more vulnerable to SARSCoV-2. Additionally, obesity is the main risk factor for comorbidities, such as SAH, DM, and cardiovascular disease.[9]

We found that patients who died were more likely to have cardiovascular disease and DM. Patients with hematological diseases died in 77.8% of cases, which is probably associated with the outbreak of COVID-19 in the inpatient unit during the study period. A systematic review study states that immunosuppression, DM, and malignancy were the comorbidities most strongly associated with severe COVID-19, while older age, male gender, DM, and SAH were associated with higher mortality.[15]

In our study, being a current smoker appears as an increased risk for mortality. A meta-analysis study reports that smokers were 1.4 times more likely to have severe symptoms of COVID-19 and were 2.4 times more likely to be admitted to the ICU, to require IMV, or to died when compared with non-smokers.[16]

Dyspnea was the most frequent symptom, according to a meta-analysis study.[8] The incidence rate of dyspnea was significantly higher in patients with severe or critical COVID-19.[8] Fever and dry cough are also among the most common symptoms.[17-18]

The median time from the onset of symptoms to hospitalization was five days, shorter than in an Italian study,[7] which was 10 days; and until ICU admission was seven days, also shorter than the average time described by study Chinese,[10] which was nine days. The median length of hospital stay was 20 days, similar to that described in the same Chinese study.[10] The median length of stay in the ICU was 12 days, as shown in some international studies.[7, 10]

Lymphopenia was found in 54.9%, high d-dimer was found in 81.4%, and high C-reactive protein in 61.1%. Another study found an incidence of lymphopenia in up to 83% of hospitalized patients with COVID-19, elevated values of D-dimers present in 43% to 60% of patients. The study, however, stated that most of these laboratory characteristics are not specific and are also common in pneumonia.[19]

More severe laboratory abnormalities were associated with more severe infection. D-dimer and, to a lesser extent, lymphopenia appear to have the strongest associations of poor prognosis. In another study, most patients had elevated C-reactive protein levels (83.5%), elevated D-dimer (73.3%), lymphopenia (70.3%).[8]

Invasive mechanical ventilation (IMV) was used in 88% of patients, similar to that found in the literature [11] of 83.9%, and higher than the findings in a recent study,[10]

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which were 67.7%. This difference in relation to the data is probably related to the 45 studies eligible for the meta-analysis, which encompass 17 countries on 4 continents, highlighting the differences in health systems, availability of equipment, and populational characteristics.[10] The median time of IMV in our study was 13 days, similar to an Italian study.[7]

We also identified that 25.7% were treated with renal replacement therapy, higher than that reported in a study,[10] which was 16.9%, and close to 22%.[8] Extracorporeal membrane oxygenation (ECMO) therapy was indicated for only 0.3% of patients, while authors[10] observed 6.4% in their study. The difference may be associated with the fact that the ICU of the HNSC does not have ECMO therapy, requiring the transfer of patients who need this treatment, causing fewer patients to use this therapy.

Among the outcomes, we found ARDS in 42% of the patients and shock in 34.9%. Research carried out in a similar period reported ARDS in 60% of cases and shock in 32%.[8]

Researchers identified that 71% of COVID-19 patients received antibiotics, although only 4% had confirmed bacterial co-infection. Most of the studied patients were admitted to the ICU (93%) and intubated (95%).[20] In our study, nosocomial infection occurred in 40.6% of patients, and antibiotics were used in 97.8%, a high rate – also found in other studies, in which antimicrobial therapy was administered to 94.6% of patients with severe COVID-19 infection.[10] The increasing use of antibiotics may be associated with critically ill patients with possible secondary infections.[19]

Once hospitalized to the ICU with COVID-19 infection, the duration of ICU and hospital admission was prolonged, a fact that led to enormous strains in the provision of critical care. The clinical and laboratory characteristics, as well as the outcomes caused by the disease in our study are similar to those found in others.[7-9,19] The variables independently associated with higher mortality (smoking, use of vasoactive amines, and hyperkalemia at hospital admission), seem to be related to local characteristics and to a population of critically ill patients, not being a frequent finding in other studies.[10, 15]

The strengths of this study are the number of patients and the period of hospitalization, which covered the first six months of the pandemic in the state of Rio Grande do Sul, Brazil. Data were obtained via a detailed review of medical records and were subjected to periodic audits. Some limitations of this research are the impossibility of determining some variables, such as body mass index (inherent in ICU patients) and the severity of comorbidities, in addition to the absence of some data in the records of some patients, mainly laboratory and imaging findings.

Our study helps to explore this serious disease, to know the clinical characteristics and outcomes of patients with COVID-19 in the ICU of the HNSC. It will contribute to the organization of care routines and protocols in ICUs in Brazil, toward the change and optimization of conducts based on scientific knowledge and in the formation of specialized and reference services for the care of patients with the disease.

Mortality was high in critically ill patients admitted to the adult ICU of the HNSC, a reference for COVID-19 in the state of Rio Grande do Sul, in addition to being associated with advanced age, being a current smoker, use of vasoactive amines, and hyperkalemia at hospital admission.

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AUTHOR'S CONTRIBUTION

Andresa Fontoura Garbini, Daniela dos Reis Carazai, Fernanda Costa dos Santos, Raquel Lutkmeier and **Veridiana Baldon dos Santos contributed** to the conception, design of the article, analysis and writing of the article.

Rafaela dos Santos Charão de Almeida and **André Klafke** contributed to the planning and design of the article, review and final approval of the article.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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