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Critical Factors Associated with Morbimortality in COVID-19 Patients Attended at a Brazilian Public Hospital: a Cross-Sectional Study

Fatores Críticos Associados à Morbimortalidade em Pacientes com COVID-19 Atendidos em um Hospital Público Brasileiro: um Estudo Transversal

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Abstract

The association between death from Covid-19 and case management, especially in small and medium-sized municipalities, is still uncertain. To analyze sociodemographic, clinical, and pharmacological factors associated with death in patients with Coronavirus Disease 2019 (COVID-19), from a Brazilian referral public hospital. This is a cross-sectional study, with data from the hospital records of patients (≥ 18 years old) diagnosed with COVID-19, from March 2020 to March 2021. The sample was classified according to the clinical outcome into two groups (death and discharge), among which statistical associations were performed with the variables of interest, with a 5% significance level. Factors such as need for intensive care, use of mechanical ventilation, and total length of hospital stay was related to higher hospital mortality, as well as the permanence of changes in clinical laboratory testing, including lactic acid, D-dimer, markers of hepatic and renal function, C-Reactive protein, anemia, leukocytosis, lymphopenia, thrombocytopenia, pH, and blood oxygen saturation (SpO_2) ($P < 0.05$). Medications used most frequently in the studied hospital for the treatment of COVID-19, such as enoxaparin, dexamethasone, ivermectin, acetylcysteine, chloroquine, and clarithromycin were correlated with morbimortality ($P < 0.05$). Clinical outcome was influenced by patient-related factors, such as age and comorbidities, however, therapeutic interventions and the choice of medication also impacted morbimortality. These results reinforce the need for preventive actions and adequate clinical protocols in the treatment of hospitalized COVID-19 patients.

Keywords: COVID-19. SARS-CoV-2. Therapeutic. Mortality.

Resumo

A associação entre o óbito pela Covid-19 e o manejo dos casos, principalmente em municípios de pequeno e médio porte, ainda é incerta. Analisar os fatores sociodemográficos, clínicos e farmacológicos associados à morte em pacientes com a doença do Coronavírus 2019 (COVID-19) em um hospital público brasileiro de referência. Trata-se de um estudo transversal realizado com dados dos prontuários de pacientes (≥ 18 anos) diagnosticados com COVID-19 no período de março de 2020 a março de 2021. A amostra foi classificada de acordo com o desfecho clínico em dois grupos (óbito e alta) e foram realizados testes de associação estatística com as variáveis de interesse com nível de significância de 5%. Fatores como necessidade de terapia intensiva, uso de ventilação mecânica e tempo total de internação estiveram relacionados com maior mortalidade hospitalar, assim como a permanência de alterações nos exames laboratoriais clínicos, incluindo ácido lático, D-dímero, marcadores de função hepática e renal, proteína C reativa, anemia, leucocitose, linfopenia, trombocitopenia, pH e saturação de oxigênio no sangue (SpO2) (P < 0,05). Os medicamentos utilizados com maior frequência no hospital para o tratamento de COVID-19, como enoxaparina, dexametasona, ivermectina, acetilcisteína, cloroquina e claritromicina, foram correlacionados com morbimortalidade (P < 0,05). O desfecho clínico foi influenciado por fatores relacionados ao paciente, como idade e comorbidades, porém as intervenções terapêuticas e a escolha dos medicamentos também impactaram na morbimortalidade. Esses resultados reforçam a necessidade de ações preventivas e protocolos clínicos adequados no tratamento de pacientes hospitalizados com COVID-19.

Palavras-chave: *COVID-19. SARS-CoV-2. Tratamento. Mortalidade.*

1 Introduction

The new coronavirus was first identified in Wuhan, China, in December 2019, and Coronavirus Disease 2019 (COVID-19) assumed the relevance of a pandemic risk, which was later established as such, and is not controlled yet. This virus belongs to the Coronaviridae family, currently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) due to its similarity to the virus that caused the SARS epidemic in 2003, the SARS-CoV.[1,2]

SARS-CoV-2 has caused asymptomatic and symptomatic conditions of several degrees of severity and high morbidity and mortality worldwide, with about 695,000 deaths in Brazil and about 6,700,000 worldwide, so far.[3,4] Misconceptions and obstacles in clarifying the epidemiological and clinical aspects of COVID-19, in addition to pharmacological management, made it difficult to control the pandemic.[5] The need for daily health surveillance of the disease has become essential to allow for changes in prevention, treatment, and control recommendations, since some clinical behaviors and procedures adopted in the health system are still questionable.[3,6]

The COVID-19 clinical manifestations include fever, dry cough, fatigue, and loss of taste and smell.[7] However, less common symptoms, such as headache and sore throat have been observed among patients infected by emerging variants.[6] Similar to SARS-CoV, the interaction of SARS-CoV-2 with the infected cell involves the fusion of its spike protein with the angiotensin-converting enzyme 2 (ACE2) receptor, widely expressed in different cells, which can affect several organs and tissues, especially cardiovascular and respiratory systems.[8,9]

Despite the approval of drugs, such as tixagevimab+cilgavimab, COVID-19 treatment still presents major challenges to clinical management. Many treatments were based on experience with similar viruses[10] which directed the actions against the disease, to increase epidemiological surveillance and health care.[11] Non-pharmacological approaches, such as social distancing and isolation, as well as the use of masks, were implemented in several countries, greatly reducing the severe consequences of the pandemic.[12]

Currently, the virus continues to spread and mutate, which can affect the effectiveness of available vaccines. In addition, it must be considered that part of the population has not received vaccines, either by choice or by contraindication, and that immunocompromised people are more prone to a lower immune response to vaccination, making them more vulnerable to severe forms of the disease. Therefore, the visibility of the determinants of clinical outcomes is still necessary to support the evolution of the dynamics of case management, especially in small and medium-sized inland municipalities, which generally have limited access to health resources and are less frequently the setting for scientific studies. Thus, the objective of this study is to analyze the sociodemographic, clinical and pharmacological factors associated with death in patients with COVID-19, from a Brazilian public reference hospital.

2 Material and Methods

2.1 Ethical approval and statement

The study project was submitted and approved by the Federal University of Alfenas institutional review board (CAAE: 33543520.8.0000.5142, opinion # 4.697.690), in line with the ethical standards from the Helsinki Declaration. Accesses to medical record were only possible after obtaining a signed informed consent form.

2.2 Study location

The study was carried out in a hospital that serves the Brazilian Unified Health System (SUS), the *Santa Casa de Caridade Nossa Senhora do Perpétuo Socorro* (*Santa Casa de Alfenas*), a reference hospital in the treatment of COVID-19 in the municipalities of the micro-regions of the Regional Health Superintendence of Alfenas-Minas Gerais, Brazil.

2.3 Study design

This is a cross-sectional study carried out with adult individuals (≥18 years) who have received a positive laboratory diagnosis for COVID-19 (SARS-CoV-2 antigen diagnostic or reverse transcription polymerase chain reaction [RT-PCR] test, associated with clinic symptoms) in the aforementioned hospital. The inclusion criteria were patients admitted at the *Santa Casa de Alfenas* from March 1st, 2020, to March 1st, 2021, diagnosed with COVID-19, and who presented the data of interest in the medical records. The exclusion criteria were patients who did not present records of the investigated variables, due to transfer to other units and/or lack of reports at the institution, and discarded cases of SARS-CoV-2 infection. Non-probability sampling was used, for convenience, consisting of all patients hospitalized in the pre-established study period. Data collection was carried from May 10th, 2021, to December 10th, 2021.

The sample was classified into two groups, according to the outcome: death and hospital discharge. The data of interest (indicators on hospital admission, hospitalization, and outcomes) were collected from the medical records (electronic and/or manual) of the patients, available at the health unit after death or hospital discharge. The indicators at hospital admission were sex, age, race, marital status, pharmacotherapy prior to admission, presence of comorbidities, signs and symptoms, vital signs, and time from onset of symptoms to admission. The indicators in hospital admission were clinical evolution, pharmacotherapy prescribed during hospitalization, clinical laboratory testing (coagulation tests, renal and hepatic function, blood count, blood gas analysis, and acute phase plasma proteins), length of hospitalization, number of days of non-invasive mechanical ventilation (when used), number of days of invasive mechanical ventilation (when used), and number of days in the intensive care unit (ICU, when admitted). The research considered the death as primary outcome and tried to identify the characteristics of hospitalized patients, as well as other factors that determined morbidity and mortality within the hospital.

2.4 Data analysis

Categorical variables were described as absolute and relative frequencies and quantitative variables as median with minimum and maximum values. Normality was assessed by the Shapiro-Wilk test. Crossings in categorical variables were performed using the chi-square (χ^2) or Fisher's exact test, and when quantitative variables were involved, the Mann-Whitney U test (nonparametric test) was used, with a 5% significance level for all the comparisons.

Analysis of correlations between drugs and outcome were obtained using Spearman's correlation coefficient. Correlation coefficients were tested for the null hypothesis of correlation equal to zero with a 5% significance level. In the multivariate approach, a Principal Component Analysis (PCA) was

performed with the total doses of the drugs and insertion of the supplementary variable referring to the outcome. In the case of pharmaceutical products that were drug combinations, each drug was analyzed separately. All analyses were performed using the R 4.1.2 software (R Core Team, 2021), except for the PCA which was performed using the FactoMineR package (2008).

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was used as a guideline for reporting the study.[13]

3 Results and Discussion

During the study, 239 patients were hospitalized with respiratory syndrome characteristic of COVID-19; 22 did not meet the inclusion criteria. Therefore, the sample was composed of 217 patients who required hospital care as a result of the disease, out of which 80 (36.9%) died and 137 (63.1%) were discharged from the hospital. Table 1 shows the sociodemographic and clinical characteristics associated with death or hospital discharge outcomes. The median age of all the hospitalized patients was 64 years (21–97), 56.2% were male, 82.0% self-reported white skin color, and 52.5% were married or had partners. Out of the total number of patients, 160 (74%) had at least one underlying chronic disease, 135 (62.2%) had previously used medication for the treatment of these diseases, and 31 (14.0%) presented an unhealthy lifestyle. The most common comorbidities were systemic arterial hypertension (SAH) (55.3%), diabetes mellitus (DM) (23%), hypothyroidism (17.5%), and heart disease (16.6%).

Table 1 - Sociodemographic and clinical characteristics of COVID-19 patients (n = 217) associated with outcomes

VARIABLES		**PATIENT OUTCOMES**				
Qualitative	**F (%)**	**Death**		**Hospital Discharge**		**p-value**
		F	**%**	**F**	**%**	
Biological sex						
Male	122(56.2)	44	55.0	78	56.9	0.782
Female	95(43.8)	36	45.0	59	43.1	
Race						
Leucoderm (white)	178(82.0)	65	81.2	113	82.5	0.820
Feoderm/ Melanoderm (brown/black)	39(18.0)	15	18.8	24	17.5	
Marital status						
Married/ Partner	114(52.5)	38	47.5	76	55.5	0.543
Single	44(20.3)	16	20.0	28	20.4	
Widow(er)	39(18.0)	18	22.5	21	15.3	
Divorced	20(9.2)	08	10.0	12	8.8	
Previous medications						
Yes	135(62.2)	58	72.5	77	56.2	**0.017**
No	82(37.8)	22	27.5	60	43.8	
Chronic diseases						
Yes	160(73.7)	67	83.8	93	67.9	**0.010**
No	57(26.3)	13	16.2	44	32.1	
SAH						
Yes	120(55.3)	52	65.0	68	49.6	**0.028**
No	97(44.7)	28	35.0	69	50.4	
Diabetes mellitus						
Yes	50(23.0)	23	28.7	27	19.7	0.127
No	167(77)	57	71.2	110	80.3	
Hypothyroidism						
Yes	38(17.5)	18	22.5	20	14.6	0.140
No	179(82.5)	66	77.5	117	85.4	
Heart diseases						
Yes	36(16.6)	20	25	16	11.7	**0.011**
No	181(83.4)	60	75	121	88.3	
Lung diseases						
Yes	25(11.5)	11	13.8	14	10.2	0.432
No	192(88.5)	69	86.2	123	89.8	
Neurological diseases						
Yes	30(13.8)	14	17.5	16	11.7	0.231
No	187(86.2)	66	82.5	121	88.3	
Kidney diseases						
Yes	11(5.1)	06	7.5	05	3.6	0.219†
No	206(94.6)	74	92.5	132	96.4	
Obesity						
Yes	8(3.7)	03	3.8	05	3.6	0.619†
No	209(96.3)	77	96.2	132	96.4	
Not healthy life habits						
Yes	30(13.8)	08	10	22	16.1	0.212
No	187(86.2)	72	90	115	83.9	
Smoking						
Yes	25(11.5)	07	8.8	18	13.1	0.329
No	192(88.5)	73	91.2	119	86.9	
Alcoholism						
Yes	8(3.7)	02	2.5	06	4.4	0.478
No	209(96.3)	78	97.5	131	95.6	
Need for ICU admission						
Yes	103(47.5)	77	96.2	26	19	**<0.001**
No	114(52.5)	03	3.8	111	81	
NIMV						
Yes	187(86.2)	76	95	111	81	**0.004**
No	30(13.8)	04	05	26	19	
IMV						
Yes	75(34.6)	65	81.2	10	7.3	**<0.001**
No	142(65.4)	15	18.8	127	92.7	
Quantitative	Median (MMV)	Death		Hospital discharge		p-value
		Median (MMV)		Median (MMV)		
Age (years)	64(21-97)	73(34-97)		57(21-90)		**<0.001**‡
Interval symptoms onset - admission	07(01-16)	06(02-15)		07(01-16)		0.298‡

VARIABLES		PATIENT OUTCOMES				
Qualitative	F (%)	Death		Hospital Discharge		p-value
		F	%	F	%	
Length of total hospital stay (days)	06(01-40)	06(01-40)		04(01-30)		**<0.001**‡
Length of ICU stay (days)	07(01-39)	09(01-39)		05(01-32)		**0.031**‡
Length of NIMV (days)	03(01-21)	03(01-14)		04(01-21)		0.488‡
Length of IMV (days)	08(01-37)	07(01-37)		10(01-20)		0.888‡

Caption: n-sample; F-frequency; SAH-Systemic arterial hypertension; NIMV-Noninvasive mechanical ventilation; IMV-invasive mechanical ventilation; ICU-Intensive Care Unit; MMV-minimum and maximum values

Note: p-values were calculated using the χ^2 or Fisher's test (†) and the Mann-Whitney U test (‡)

Source: The authors.

Table 1 shows that there was no statistic significant difference among biological sex, race, and marital status for mortality. Patients who died were older [73 years (45–97)] than patients who were discharged [53 years (21–86)] (p<0.001). Chronic diseases were related to the highest percentage of deaths (p < 0.001), with SAH and heart diseases associated with higher mortality. The previous use of medication for comorbidity treatment was associated with the outcome of death (p = 0.017). The median time between the onset of symptoms and hospitalization was seven (01–16) days and the length of stay was six (01–40) days. There was no significant difference in onset of symptoms and hospitalization of patients who died (P > 0.05), however, there was a higher median length of stay for these patients (p < 0.001). During hospitalization, 47.5% of the patients required ICU care, 86.2% used non-invasive oxygen therapy, and 34.6% used invasive oxygen therapy, with a median duration of seven (01–39), three (01–21), and eight (01–31) days, respectively. Patients admitted to the ICU and who received non-invasive (86.2%) and invasive mechanical ventilation (34.6%) showed a greater association with the outcome of death (p < 0.05). The highest median length of stay in the ICU was also related to mortality (p = 0.031) (Table 1).

Table 2 shows the symptoms and vital signs at hospital of admission associated with the death outcome. On admission, difficulty breathing (82%), cough (51.6%), and fever (37.3%) were the most common symptoms, but only fever showed a statistically significant relationship with death (p = 0.008). Body aches were reported by 29.5% of the sample, and this symptom was associated with patient survival (discharge) (p = 0.003). We observed a slight tachypnea [21 bpm (14–89)] and a decreased oxygen saturation levels [94% (55–99)], clinically consistent with dyspnea. Increased body temperature was associated with death (p = 0.005).

Table 2 - Symptoms and vital signs of COVID-19 patients (n = 217) at admission associated with outcomes

Variables Hospital admission		Patient Outcomes				
Symptoms	F (%)	Death		Hospital discharge		p-value
		F	%	F	%	
Dyspnea						
Yes	178(82.0)	70	87.5	108	78.8	0.109
No	39(18.0)	10	12.5	29	21.2	
Cough						
Yes	112(51.6)	35	43.8	77	56.2	0.077
No	105(48.4)	45	56.2	60	43.8	
Fever						
Yes	81(37.3)	24	30	57	41.6	**0.008**
No	136(62.7)	36	70	80	58.4	
Fatigue/weakness						
Yes	72(33.2)	26	32.5	46	33.6	0.871
No	145(66.8	54	67.5	91	66.4	
Body aches						
Yes	64(29.5)	14	17.5	50	36.5	**0.003**
No	153(70.5)	66	82.5	87	63.5	
Loss of taste or smell						
Yes	39(18)	13	16.2	26	19	0.614
No	178(82)	67	83.8	111	81	
Nausea/vomit/diarrhea						
Yes	31(14.3)	9	11.2	22	16.1	0.329
No	183(85.7)	71	88.8	115	83.9	
Vital signs	Median (MMV)	Death		Hospital discharge		p-value
		Median (MMV)		Median (MMV)		
Body temperature (NR 35.4ºC - 37.2ºC)	36(32-40)	36(34-40)		36(32-39)		**0.005**‡
Heart rate (NR 50 - 90 bpm[a])	85(23-180)	103(48-180)		78(23-152)		0.105‡
Respiratory rate (NR 16 - 20 bpm[b])	21(14-89)	21(12-89)		21(14-36)		0.123‡
Systolic blood pressure (NR 100 - 140 mmHg)	120(54-210)	120(54-210)		120(54-120)		0.407‡
Diastolic blood pressure (NR 60 - 90 mmHg)	80(38-150)	80(38-150)		80(51-136)		0.128‡
SpO_2 (NR 95 - 100%)	94(55-99)	94(60-98)		93(55-99)		0.296‡

Caption: n-sample; F-frequency; NR - Normal range; MMV - minimum and maximum values; SpO_2 - oxygen saturation

Note: p-values were calculated using the $\chi 2$ test and the Mann-Whitney U test (‡); a-beats per minute; b-breaths per minute

Source: The authors.

Table 3 shows the hematological and biochemical parameters at hospital admission and before death or discharge. At hospital admission, most patients presented lymphopenia, increased prothrombin time (PT) and activated partial thromboplastin time (aPTT), increased lactic acid and C-Reactive Protein (CRP). Additionally, 43.4% presented hemoglobin below the normal and 32.7% had leukocytosis. Increased D-dimer, urea, creatinine, or CRP levels were associated with the death outcome ($P < 0.05$) (Table 3). Before the patient's death or hospital discharge, we observed that low hemoglobin ($p = 0.001$), leukocytosis ($p < 0.001$), lymphopenia ($p = 0.032$), decreased platelets ($p < 0.001$), pH, and blood oxygen saturation (SpO_2) ($p < 0.001$) and increased D-dimer ($p = 0.032$), AST ($p = 0.024$), urea ($p < 0.001$), creatinine ($p < 0.001$), lactic acid ($p = 0.007$), and CRP ($p = 0.001$) levels were related to greater hospital mortality (Table 3).

Table 3 - Hematological and biochemical parameters of COVID-19 patients on admission and before death or hospital discharge

Variables	F	F (%)	Patient Outcomes				p-value
			Death		Hospital discharge		
			F	%	F	%	
Hospital admission							
Hemoglobin (NR M:13.5-17.5 g/dL; W:11.5-15.0 g/dL)	196						
Normal range		111(56.0)	36	48.6	75	61.5	0.079
Value below the normal		85(43.4)	38	51.4	47	38.5	
White blood cells (NR 4.000-10.000/mm^3)	196						
Normal range		116(59.2)	38	51.4	78	63.9	0.174
Value below the normal		16(8.2)	06	8.1	10	8.2	
Value above the normal		64(32.7)	30	40.5	64	27.9	
Lymphocytes (NR 20-30%/mm^3)	87						
Normal range		02(2.3)	00	0.0	02	4.9	0.207
Value below the normal		84(96.6)	45	97.8	39	46.4	
Value above the normal		01(2.2)	01	2.2	00	0.0	
Platelets (NR 150.000-450.000/ mm3)	195						
Normal range		164(84.1)	61	83.6	103	84.4	0.873
Value below the normal		31(15.9)	12	16.4	19	15.6	
PT (NR 11 - 13 s)	60						
Normal range		04(6.7)	03	6.7	1	6.7	1.000
Value above the normal		56(93.3)	42	93.3	56	93.3	
aPTT (NR 25 - 35 s)	58						
Normal range		26(44.8)	19	42.2	07	53.8	0.458
Value above the normal		32(55.2)	26	57.8	06	46.2	
D-dimer (NR 0.5 µg/mL)	106						
Normal range		57(53.8)	19	40.4	38	64.4	**0.014**
Value above the normal		49(46.2)	28	59.6	21	35.6	
ALT (NR M: 0-58 UI; W: 0-40 UI)	125						
Normal range		91(72.8)	39	81.2	52	67.5	0.094
Value above the normal		34(27.2)	09	18.8	25	32.5	
AST (NR M: 0-46 UI; W: 0-40 UI)	128						
Normal range		77(60.2)	29	59.2	48	60.8	0.860
Value above the normal		51(39.8)	20	40.8	31	39.2	
Urea (NR 10-50 mg/dL)	192						
Normal range		127(66.1)	36	48.6	91	77.1	**<0.001**
Value above the normal		65(33.9)	38	51.4	27	22.9	
Creatinine (NR 0.4-1.3 mg/dL)	112						
Normal range		91(81.2)	28	63.6	63	92.6	**<0.001**
Value above the normal		21(18.8)	16	36.4	05	7.4	
Lactate (NR 0.5-2.2 mmol/L)	109						
Normal range		94(86.2)	41	83.7	53	88.3	0.482
Value above the normal		15(13.8)	08	16.3	07	11.7	
CRP (NR 0-5mg/L)	189						
Normal range		19(10.1)	01	1.4	18	15.7	**0.001**
Value above the normal		170(89.9)	73	98.6	97	84.3	
pH (NR 7.35 - 7.45)	201						
Normal range		96(47.8)	42	56.8	54	42.5	**<0.001**
Value below the normal		22(10.9)	15	20.3	07	5.5	
Value above the normal		83(41.3)	17	23	66	52	
pO_2 (NR 80-100 mmHg)	199						

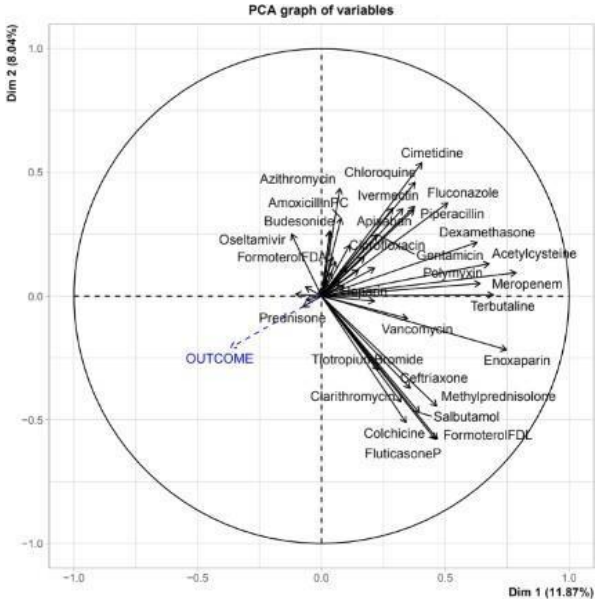
Variables	F	F (%)	Patient Outcomes				p-value
			Death		Hospital discharge		
			F	%	F	%	
Normal range		26(13.1)	13	17.6	13	10.4	0.327
Value below the normal		148(74.4)	53	71.6	95	76.0	
Value above the normal		25(12.6)	08	10.8	17	13.6	
SpO_2 (NR 96-100%)	193						
Normal range		53(27.5)	16	22.2	37	30.6	0.208
Value below the normal		140(72.5)	56	77.8	84	69.4	
Hospital discharge or before death							
Hemoglobin (NR M:13.5-17.5 g/dL; W:11.5-15.0 g/dL)	167						
Normal range		56(33.5)	13	19.1	43	43.4	**0.001**
Value below the normal		111(66.5)	55	80.9	56	56.6	
White blood cells (NR 4.000-10.000/mm^3)	166						
Normal range		95(57.2)	23	34.8	72	72.0	**<0.001**
Value above the normal		71(42.8)	43	65.2	28	28.0	
Lymphocytes (NR 20-30%/ mm^3)	80						
Normal range		05(6.2)	02	4.3	03	9.1	**0.032**
Value below the normal		74(92.5)	45	95.7	29	87.9	
Value above the normal		0.1(1.2)	00	0.0	01	3.0	
Platelets (NR 150.000-450.000/ mm3)	165						
Normal range		130(78.8)	42	63.6	88	88.9	**<0.001**
Value below the normal		35(21.2)	24	36.4	11	11.1	
PT (NR 11 - 13 s)	66						
Normal range		06(9.1)	3	5.4	03	30	1.000
Value above the normal		60(90.9)	53	94.6	07	70	
aPTT (NR 25 - 35 s)	64						
Normal range		17(26.6)	12	23.1	05	41.7	0.189
Value above the normal		47(73.4)	40	76.9	07	58.3	
D-Dimer (NR 0-0.5 µg/mL)	122						
Normal range		63(51.6)	19	39.6	44	59.5	**0.032**
Value above the normal		59(48.4)	29	60.4	30	40.5	
ALT (NR M: 0-58 UI; W: 0-40 UI)	125						
Normal range		69(55.2)	29	60.4	40	51.9	0.354
Value above the normal		56(44.8)	19	39.6	37	48.1	
AST (NR M: 0-46 UI; W: 0-40 UI)	126						
Normal range		66(52.4)	19	39.6	47	60.3	**0.024**
Value above the normal		60(47.6)	29	60.4	31	39.7	
Urea (NR 10-50 mg/dL)	192						
Normal range		101(52.6)	11	14.7	90	76.9	**<0.001**
Value above the normal		91(47.4)	64	85.3	27	23.1	
Creatinine (NR 0.4-1.3 mg/dL)	186						
Normal range		123(6.1)	28	38.9	95	83.3	**<0.001**
Value above the normal		63(33.9)	44	61.1	19	16.7	
Lactate (NR 0.5-2.2 mmol/L)	120						
Normal range		100(83.3)	42	73.7	58	92.1	**0.007**
Value above the normal		20(16.7)	15	26.3	05	7.9	
CRP (NR 0-5mg/L)	189						
Normal range		19(10.1)	01	1.4	18	15.7	**0.001**
Value above the normal		170(89.9)	73	98.6	97	84.3	
pH (NR 7.35 - 7.45)	187						
Normal range		67(35.8)	15	21.1	52	44.8	**<0.001**
Value below the normal		56(29.9)	47	66.2	09	7.8	
Value above the normal		64(34.2)	09	14.1	55	47.4	
pO_2 (NR 80 - 100 mmHg)	177						
Normal range		40(22.6)	16	23.2	24	22.2	0.191
Value below the normal		111(62.7)	47	68.1	64	59.3	
Value above the normal		26(14.7)	06	8.7	26	14.7	
SpO_2 (NR 96 - 100%)	175						
Normal range		59(33.7)	11	15.9	48	45.3	**<0.001**
Value below the normal		116(66.3)	58	84.1	58	54.7	

Caption: F-frequency; NR-Normal range; M-Men; W-Women; PT-Prothrombin Time; aPTT-Activated Partial Thromboplastin Time; ALT-Alanine Transaminase; AST-Aspartate Transaminase; CRP-C-Reactive Protein; pO_2- Oxygen pressure; SpO_2-Oxygen saturation
Note: p-values were calculated using the χ^2 test

Source: The authors.

Figure 1 highlights the statistical relationship between the medications used in the COVID-19 treatment (or its complications) and the clinical outcomes (death or hospital discharge). Each drug was represented by a vector, as well as the outcome, highlighted in dashed. The direction in which the dashed arrow points indicates hospital discharge, whereas the opposite direction indicates death. Prednisone and acetylsalicylic acid are associated with hospital discharge, whereas chloroquine, cimetidine, dexamethasone, and others are correlated with death. The correlations (and their respective p-values), showed in Figure 1, between drugs and outcomes were also tabulated (Table 4). Enoxaparin was the most prescribed drug (88%) during the study period, while the most prescribed antibiotics were azithromycin, clarithromycin, and ceftriaxone. The most used anti-inflammatory drugs were dexamethasone, methylprednisolone, and colchicine. The antiviral oseltamivir was used by 37% of the patients and the antimalarial chloroquine by 28% of the patients. Ivermectin (73%) and acetylcysteine (65%) were also extensively administered. We noticed that drugs used more prevalently in the hospital unit for the treatment of COVID-19 during the study period — such as enoxaparin, dexamethasone, ivermectin, acetylcysteine, chloroquine, and clarithromycin — were correlated with morbidity and mortality in the municipality ($P < 0.05$) (Table 4).

Figure 1 - Space of variables in a principal component analysis (PCA): pharmacological treatments used in COVID-19 patients *versus* clinical outcomes



Source: The authors.

Table 4 Correlations between medications used in COVID-19 patients and clinical outcomes

PRESCRIBED MEDICATIONS (classes[1])	F (%)	Correla-tions	p-value
ANTIMICROBIALS			
Antibacterial			
Amikacin	03(1.4)	-0.1387	**0.038**
Amoxicillin + potassium clavulanate	09(4.2)		
Amoxicillin		-0.1174	0.079
Potassium clavulanate		-0.1295	0.081
Ampicillin	01(0.5)	-0.0881	0.189
Azithromycin	111(51)	0.0022	0.974
Cefepime	04(1.8)	-0.1221	0.068
Ceftriaxone	98(45)	-0.1105	0.099
Ciprofloxacin	06(2.7)	-0.1130	0.092
Clarithromycin	53(24)	-0.1479	**<0.001**
Clindamycin	04(1.8)	0.0762	0.2558
Gentamicin	03(1.4)	-0.0984	0.142
Levofloxacin	21(9.7)	-0.0725	0.280
Meropenem	29(13.4)	-0.2643	**<0.001**
Oxacillin	02(0.9)	-0.0935	0.163
Piperacillin + tazobactam	43(19.8)		
Piperacillin		-0.2672	<0.001
Tazobactam		-0.2897	<0.001
Polymyxin	13(5.9)	-0.1973	**<0.001**
Vancomycin	34(15.7)	-0.0954	0.155
Antifungal			
Amphotericin B	01(0.5)	-0.0881	0.1888
Fluconazole	15(6.9)	-0.2126	**0.0014**
Antiviral			
Acyclovir	03(1.4)	-0.0340	0.613
Oseltamivir	80(37)	0.1189	0.0758
Antiparasitic			
Chloroquine	60(28)	-0.2309	**<0.001**
Hydroxychloroquine	05(2.3)	0.0995	0.138
Ivermectin	159(73)	-0.1960	**0.003**
ANTI-INFLAMMATORY			
Dexamethasone	174(80)	-0.2568	**<0.001**
Formoterol fumarate dihydrate + budesonide (Alenia)	06(2.8)		
Formoterol fumarate dihydrate		-0.0828	0.217
Budesonide		-0.0828	0.217
Formoterol fumarate dihydrate + fluticasone propionate (Lugano)	04(1.8)		
Formoterol fumarate dihydrate		0.0704	0.294
Fluticasone propionate		0.0760	0.257
Hydrocortisone	22(10)	0.0328	0.6252
Methylprednisolone	67(30)	-0.1029	0.125
Prednisone	07(3.2)	0.1152	0.085
Tenoxicam	01(0.5)	0.0509	0.449
ANTICOAGULANT			
Apixaban	01(0.5)	-0.0881	0.189
Enoxaparin	192(88.4)	-0.2372	**<0.001**
Heparin	22(09)	0.0283	0.674
BRONCHODILATOR			

PRESCRIBED MEDICATIONS (classes[1])	F (%)	Correla-tions	p-value
Salbutamol	46(21)	-0.2647	**<0.001**
Tiotropium bromide	05(2.3)	0.0569	0.397
Terbutaline	79(36)	-0.3553	**<0.001**
ANALGESIC			
Acetylsalicylic acid (ASA)	06(2.8)	0.0865	0.197
MISCELLANEOUS			
Acetylcysteine	140(65.5)	-0.3553	**<0.001**
Cimetidine	35(14.7)	-0.2360	**<0.001**
Colchicine	57(26)	-0.1232	0.066
Dexchlorpheniramine	01(0.5)	0.0509	0.449
Dobutamine	06(2.8)	-0.1563	**0.019**
Tocilizumab	01(0.5)	-0.0881	0.189
Tranexamic acid	06(2.8)	-0.1606	**0.016**

Caption: F-frequency

Note: positive (significant) correlations indicate a correlation with hospital discharge and negative (significant) correlations indicate a correlation with death outcome. [1] Considering the main/most common use

Source: The authors.

Several clinical-epidemiological characteristics may be associated with increased severity and/or mortality of COVID-19.[14] The reasons for the different clinical outcomes may be multifactorial and include biological, environmental, and social factors. The analysis of these elements is important to direct public health policy efforts, to guide clinical care, and to predict the need for surveillance, prevention, and further intervention in specific populations.[(15)] In our study, outcome of COVID-19 patients was influenced by patient-related factors, such as age and comorbidities, corroborating the literature;[16,17] additionally, therapeutic interventions and the choice of medication also affected morbimortality. These results reinforce the need for preventive actions and adequate clinical protocols in the treatment of hospitalized COVID-19 patients.

According to previous studies, SAH and cardiovascular diseases were the main comorbidities for the progression of COVID-19.[18,19] SARS-CoV-2 can exacerbate these underlying diseases and/or induce new pathologies, due to the high inflammatory burden induced by the infection. Cardiovascular disorders have a pathophysiology related to the renin-angiotensin system (RAS) and some pharmacological inhibitors of RAS can increase the availability of ACE2 receptors (on the cell surface) that interacts with SARS-CoV-2 spike protein, increasing the entry of the virus into the lungs and heart.[18] As observed in our study, there was no significant influence of previous lung disease on morbidity and mortality. Although SARS-CoV-2 first enters the human body via the airways, infecting the lung, the high density of ACE2 receptors in the vessels greatly affect the vascular system, which is why some studies have proposed that COVID-19 is potentially more a vascular disease than a pulmonary disease.[20]

Previous studies showed that fever and cough are the most common symptoms in patients treated in a hospital unit.[21,22] In our study, the most common sign was increased body temperature, which was related to the death outcome. High temperature (fever) is a factor that activates blood clotting, which can also compromise the synthesis of red blood cells and hemoglobin, intensifying hypoxia, and decreasing SpO_2.[23] Changes in hematological and biochemical parameters can be used to predict SARS-CoV-2 infection, being an important auxiliary diagnostic tool in cases of test failures for COVID-19. Additionally, there is a relationship between these variations and mortality, implying the need to carefully monitor these parameters and early intervention.[24,25]

Table 3 shows results that are intrinsically related to the pathogenesis of the disease, indicating that at the beginning of the infection neutrophils are spared, and lymphocytes are suppressed. Notably, lymphocytes have ACE2 receptors for the SARS-CoV-2 and can be a target of infection. Generally, the intensification or maintenance of lymphopenia, with the disease evolution, shows a poor prognosis, which corroborates the associations obtained in this study. The observed leukocytosis may indicate a superinfection or some bacterial co-infection. In these cases, other inflammatory markers such as IL-6 and procalcitonin could be evaluated, in addition to microbiological tests to determine the causal infection and appropriate treatment.[(25)] C-reactive protein (CRP), induced by several inflammatory mediators, can be used as an acute biomarker of COVID-19, and the increase in its levels is also related to the increase in the severity of the disease.[24,25] Some studies state that low lymphocyte counts, D-dimer, and CRP elevations are predictive parameters of COVID-19 and may be associated with mortality.[25,26] Terpos et al.[27] reported that thrombocytopenia, elevated D-dimer, prolonged PT, and aPTT result in widespread changes in intravascular coagulation, in addition to increased levels of CRP, IL-6, lactate, and lactate dehydrogenase (LDH).

Low hemoglobin level also plays a significant role as a poor prognostic factor during hospitalization. Anemia related to death can be explained by the direct action of the virus on the erythrocyte structure (stimulating disseminated intravascular coagulation) and hemoglobin. The virus removes iron ions from red blood cells, reducing the hemoglobin's ability to transport oxygen, which leads to an abrupt drop in oxygen saturation, thus leading to dyspnea.[28] In the most severe cases, this leads to tissue hypoxia, explaining the increased lactic acid and LDH. The decreased pH and the increased CO_2 and lactate levels in the blood determine intense hypoxia, harming organs such as the liver and kidney, altering the concentrations of AST, ALT, urea, and creatinine. Moreover, the use of some drugs during hospitalization, such as clarithromycin and chloroquine, can also lead to changes in laboratory parameters, especially in liver and kidney function tests, intensifying the damage caused by the virus.[29]

Thrombocytopenia is relatively common in patients with COVID-19 and is associated with an increased risk of death. However, many patients with severe forms of the disease still do not present this finding at hospital admission[30],

which is consistent with the results obtained. The decrease in platelets can be caused by the continuous clotting process; some patients can also present thrombocytosis, since the interleukins IL-1β and IL-6 stimulate platelet proliferation This paradoxical situation, however, reflects only on the phase and not the severity of the disease.[31]

Several medications prescribed in the hospital unit of this study have indications for the treatment of other diseases. Generally, the introduction of these drugs into COVID-19 therapy is based on the pathophysiology of the disease and/or experiences with similar viruses. Changes in blood coagulation, probably caused by COVID-19 induced inflammation, leads to thrombus formation in several organs, reducing blood flow, and to the patients' worst clinical condition.[32] Thus, anticoagulants have been proposed in prophylactic doses to reduce COVID-19 mortality. However, the use in patients with a D-dimer lower than 1 µg/mL does not seem to generate benefits.[33] Conversely, these medications cause adverse reactions, serious poisoning, and contribute to increased hospitalizations, morbidity, mortality, and treatment costs.[34] Based on our results and the lack of data on the safety of therapeutic and prophylactic anticoagulation, we suggest for treatments and evaluation of parameters that indicate thrombotic changes to be individualized, considering the risk/benefit for the patient.[33,35]

Although not always recommended in viral pneumonia, antibiotics are used to prevent or to control secondary bacterial infections and sepsis. Macrolides, such as azithromycin, amikacin, and clarithromycin, are quite effective in preventing secondary lung infections in patients with viral pneumonia, in addition to demonstrating a significant anti-inflammatory effect in the airways,[(36)] justifying their use in the treatment of COVID-19. Steroid anti-inflammatory drugs, such as methylprednisolone and dexamethasone, have been shown to be effective in reducing mortality, but at low doses, since they delay viral clearance due to immunosuppressive action.[36,3)] However, we found that the use of some antibiotics, as well as the use of dexamethasone, was correlated with death, which may be linked to dose and/or other pharmacological factors.

Acetylcysteine was also widely used in the studied hospital, due to mucolytic and antioxidant properties. Several extrapulmonary organ injuries in COVID-19 may be associated with an increase in cytokines and reactive oxygen species, which worsened clinical conditions.[38] In our study, acetylcysteine was correlated with death. The administration of excess antioxidants can disable the innate phagocytic response and immune response transition, by interfering with the amount of oxidants released by neutrophils and monocytes, which are essential for an adequate immune response to pathogens.[39]

In general, the choice of medication for hospitalized COVID-19 treatment can be related to adverse effects that cause more damage to the body, contributing to prolonged hospitalization time and worse clinical prognosis, with higher risk of death. Notably, some of these medications are recommended for patients in critical condition under intensive care. Therefore, it is essential to highlight that the correlations obtained in this study do not necessarily represent cause and effect. The drug may be statistically correlated with death and not be the cause of this outcome. The interpretation of these results should be limited to the sample size, as well as factors not considered in our analyses, such as the genetic and clinical characteristics of the patients and drug interactions that can alter the drugs metabolism and, consequently, increase their toxicity.

Thus, these analyzes provide significant information on clinical management, since it demonstrates the possibility of death being correlated with pharmacological treatments. This highlights the need for greater caution in prescriptions and rational use of medications, based on the risk/benefit ratio, on the patients' characteristics as well as the monitoring of laboratory and imaging parameters, in order to avoid further damage to health and high expenses for health institutions. Moreover, the analysis of evidence will contribute to clinical decision making, and, regarding public health systems, will contribute to prevent further damage to people's health and new outbreaks of the disease.

As limitations of the study, it is recognized that the development of cross-sectional observational studies does not allow the development of causal relationships. In addition, the results from data collected from medical records are susceptible to insufficient quality of records. However, carrying out the study in accordance with the informed design made it possible to collect data for the generation of hypotheses. In addition, the option for data collection in a reference hospital in the treatment of COVID-19 minimized the risk of bias in the results.

4 Conclusion

Significant factors associated with morbidity and mortality were revealed, as well as the influence of the conditions prior to hospital admission, including advanced age, SAH and heart disease, as well as the use of some drugs and other therapeutic interventions. Medications used more frequently in the studied hospital for the treatment of COVID-19, such as enoxaparin, dexamethasone, ivermectin, acetylcysteine, chloroquine, and clarithromycin, were correlated with morbidity and mortality.

We noted that the alterations in clinical laboratory testing along the course of the disease were statistically associated with the death outcome, including anemia, leukocytosis, lymphopenia, thrombocytopenia, decreases in pH and of blood oxygen saturation (SpO_2), and elevations of D-dimer, AST, urea, creatinine, lactic acid, and CRP. In this scenario, the importance of developing individual clinical-epidemiological profiles is highlighted, as it can contribute to the understanding of the disease evolution and, consequently, to the direction of clinical decisions. Furthermore, we emphasize the need to evaluate the risk/benefit of treatments and appropriate

clinical protocols in the treatment of hospitalized patients with COVID-19 to avoid further damage to health and unnecessary expenses.

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