International Journal of Science and Technology Research Archive

ISSN: 0799-6632 (Online)

Journal homepage: https://sciresjournals.com/ijstra/

(RESEARCH ARTICLE)

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Predictive factors of mortality in COVID-19 patients: Analysis of an intensive care unit in Espirito Santo, Brazil

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International Journal of Science and Technology Research Archive, 2023, 04(01), 050–064

Publication history: Received on 18 November 2022; revised on 01 January 2023; accepted on 03 January 2023

Article DOI: https://doi.org/10.53771/ijstra.2023.4.1.0178

Abstract

Background: Coronavirus disease (COVID-19) is a global health issue that keeps testing academic efforts to cease it. Many factors are involved in progression to severe disease including metabolic and inflammatory disorders. The aim of this study is to analyze the factors associated with mortality in those admitted for COVID-19 in the Intensive Care Unit (ICU) of a hospital in Espirito Santo, Brazil.

Methods: This is a retrospective, cross-sectional study, with data collection from medical records. The primary outcome studied is mortality, categorized by length of stay in the ICU. A total of 163 patients were included in this study. The data of these patients where then separated in two groups, first with 93 discharges and second with 64 deaths. The parametric Student's T-test and the nonparametric Mann–Whitney U test for continuous data and the $\chi 2$ and Fisher's exact test for categorical data were used to compare the variables between both groups. Variables with a p-value < 0.05 (in the bivariate analysis) were submitted to the Cox Survival Hazard multivariate survival model.

Results: Bivariate analysis identified as factors on admission associated with mortality: age > 60 years, high blood pressure, diabetes mellitus, heart disease, cerebrovascular disease thrombocytopenia, lactate dehydrogenase elevation, D-dimer elevation and use of supplemental oxygen. Complications while on ICU associated with higher mortality are: mechanical ventilation, mechanical ventilation> 14 days, acute renal failure, bacterial pneumonia, post COVID-19 acute arrhythmia, bloodstream infection, acute renal injury and anemia. To exclude possible interference, a multifactorial analysis was applied with the Cox Survival Hazard proportional risk model, showing that mechanical ventilation (OR: 17.254, 95%CI 4.35-68.43, p <0.0001) and anemia (OR: 2.17, 95%CI 1.15-4.09, p<0.016) are independent variables related to mortality.

Conclusion: This study identified that anemia on admission and the need to provide mechanical ventilation during ICU stay are independent factors for predicting mortality.

Keywords: Coronavirus; SARS-CoV-2; Inflammatory markers; Severe disease; Comorbidities; Chest tomography

1 Introduction

The COVID-19 pandemic has transformed the habits of the population on a global scale. In December 2019 there were reports of pneumonia of unknown origin, with an unusual pattern, rapidly evolving with Severe Acute Respiratory Syndrome (SARS), Wuhan City, Hubei Province, China. The virus was identified as a coronavirus, SARS-CoV-2, and the disease named Coronavirus Disease 2019 (COVID-19).[1,2]

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Initially the virus spread to other provinces in China and in the coming weeks there was an accelerated spread of the virus to other countries, most notably in Europe and North America, with the declaration of a COVID-19 pandemic in March 2020 by the World Health Organization[3, 9], the same month when the first COVID-19 related death occurred in Brazil.

SARS-CoV-2 is an RNA virus of the order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae, genus Betacoronavirus, subgenus Sarbecovirus.[4]

Coronaviruses infect many animals and SARS-CoV-2 appears to be a mutation from coronaviruses present in bats and/or pangolins from China due to the genetic Yesilarity found between coronaviruses that infect these animals and SARS-CoV-2. [1]

COVID-19 is a disease that affects several organs, leading to temporary and permanent injuries, with varying degrees of tissue fibrosis, depending on the evolution of the disease. The most affected organ are lungs followed by the kidneys, heart and brain, but not limited to these. The involvement of several systems occurs both by changes related to circulation and by the expression of binding proteins in cell membranes, especially the Angiotensin Converting Enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) receptors, which are present in greater quantity in the organs of the systems mentioned above, in addition to being present in large quantities in endothelial cells. [1,5]

The SARS-CoV-2 coronavirus, upon entering the respiratory tract through the nasopharynx, tends to replicate and migrate to the lower respiratory tract. Viral replication, and especially the exacerbated inflammatory response, causes a cytokine storm, leading to direct and indirect damage to lung tissue, which can lead to dyspneic symptoms in patients with severe acute respiratory syndrome. Histopathological analysis of the lungs of coronavirus-infected patients who progressed to a severe condition showed diffuse alveolar damage, hyaline membrane formation with pneumocyte desquamation and fibrin deposits. Immunohistochemical tests showed antigen for SARS-CoV-2 present in both the upper and lower respiratory tract, as well as type I pneumocytes, type II pneumocytes and alveolar macrophages. [1,6]

Disseminated vascular coagulation in the most severe cases, associated with small vessel thrombosis, corroborates the symptoms of the respiratory, cardiovascular and urinary systems.[6]

In the cardiovascular system, the disease can lead to myocarditis, acute myocardial infarction, cerebrovascular accident, and the lesions may be caused by viral invasion into the cell or even as a result of metabolic changes related to more severe conditions with systemic hypoxia. [6,7,8]

Regarding urinary system, it can cause acute tubular necrosis by direct viral injury and by rhabdomyolysis or even cortical necrosis, leading to acute and/or chronic renal failure. [6]

This is a virus with a high transmissibility rate, with very aggressive strains, which has already caused more than 600,000 deaths in Brazil alone and 5 million worldwide.[9] Considering the global involvement and the emergence of new variants of viral strains, there is a need for an adequate understanding of the disease as well as the preparation of the health system to support this and eventual new pandemics. This research aims to identify the factors associated with mortality of patients hospitalized with COVID-19 in a Hospital in Espirito Santo, Brazil.

2 Methods

2.1 Study design

This is a retrospective, cross-sectional study, carried out by analyzing data from medical records of patients who were admitted to Intensive Care Units (ICU) at Hospital Meridional in Cariacica, Espirito Santo, Brasil. The Hospital is private and is part of an aggregated network of 06 hospitals. It attends the spontaneous demand of the emergency room and is a reference for the most complex cases. The criteria for admission of patients to the ICU at this service include at least one of the following: chest computed tomography with > 50% Ground Glass Opacity (GGO), use of oxygen therapy with a flow greater than 04 liters per minute, clear signs of acute respiratory failure.

2.2 Ethical issues

The study was approved by the Research Ethics Committee of Universidade Vila Velha (CAAE: 49128821.4.0000.5064), which is subject to the norms of the National Health Council – Ministry of Health of Brazil. The informed consents were

presented to the patient or their legal representative, online, due to the context of the pandemic, participating in the study only those in which there was agreement.

2.3 Patient selection

Data collection was carried out in the medical records of patients hospitalized from May to December 2020 in intensive care units. Inclusion criteria were patients in a cohort bed in an intensity unit with positive RT-PCT test for SARS-CoV-2 or with immunochromatographic positive SARS-CoV-2 test plus chest computed tomography with ground glass opacity. Exclusion criteria were: Terminal illness with a proposal for palliative care prior to admission, primary hospital admission due to other diseases, incomplete medical records for analysis due to hospital transfer, refusal of consent form, telephone contact was not possible or did not respond to the consent form.

Initially, the medical records of 287 patients were selected from the management software database called Epimed®. Of these, 124 patients were excluded by the exclusion criteria: 13 had a negative laboratory test for SARS-CoV-2, 02 were terminally ill patients with a proposal for palliative treatment prior to admission, 41 were hospitalized for other reasons, prior to infection, 07 were transferred to another service, 04 refused to participate. In addition, 57 patients who did not respond to telephone contacts or who did not respond to the consent form were excluded.

Clinical data were collected through individual review of electronic medical records on the MVPep® Platform. Both qualitative and quantitative data were collected, encompassing clinical, laboratory and imaging data.

2.4 Data classification

Acute kidney injury (AKI) was categorized as a serum creatinine value > 1.3 mg/dL, anemia was defined as a serum hemoglobin < 12 g/dL, leukocytosis as a total WBC count > 10,500/µL, thrombocytopenia if a platelet count < 150,000/ µL, lymphopenia <1,500/ µL, hypercapnia when Partial Pressure of Carbon dioxide (pCO2) >45 mmHg on arterial blood gases and hypoxemia when Blood Pressure of Oxygen (PaO2) < 80 mmHg on arterial blood gases and coagulopathy was defined as partial thromboplastin time (APTT) > 42 seconds or INR (international normalized ratio) >1.3 or prothrombin activation time (TAP) <70%. The results of D-dimer, ferritin, lactate dehydrogenase (LDH) and C-reactive protein (CRP) tests were collected according to their quantitative numerical value.

Pulmonary involvement on chest tomography was recorded according to the amount of ground-glass opacity in the pulmonary area and its total percentage of involvement, according to the radiologist's report. A classification of up to 25%, >25-50%, >50-75% and >75% of total lung area affected was used.

The P/F ratio (Blood Pressure of Oxygen over the Fraction of Inspired Oxygen) was calculated for all patients, and its numerical value was recorded. The fraction of inspired oxygen (FiO2) was determined according to the oxygen delivery device (nasal catheter, high-flow mask or orotracheal intubation) and the volume of oxygen delivered on each device.

2.5 Statistical Analysis

To evaluate a sample of n=163 patients (64 deaths and 99 discharges) in order to identify clinical and laboratory parameters that are associated with patient survival, considering length of stay in the ICU, descriptive and inferential statistical methods were applied.

Qualitative variables were presented by distribution of absolute and relative frequencies. Quantitative variables were presented by measures of central tendency and variation and had their normality assessed by the D'Agostino-Pearson test.

In the inferential part, the following methods were applied: (a) To assess the association between the qualitative variables and the Death outcome, the chi-square test was applied and when the restriction npq < 5 occurred, the Fisher's Exact test was applied; (b) To compare the quantitative variables, according to the Discharge and Death groups, the Student's t test was preferably applied and when any variable did not present a Gaussian distribution, the Mann-Whitney U test was applied; (c) Variables with a p-value < 0.05 (in the bivariate analysis) were submitted to the Cox Survival Hazard multivariate survival model.

An alpha error was previously set at 5% for rejection of the null hypothesis and the statistical processing was performed in BioEstat® version 5.3 and SPSS® Version 27.

The clinical variables studied were sex, age, pre-existing comorbidities at ICU admission: High Blood Pressure (HBP), Diabetes Mellitus (DM), Obesity, Chronic Obstructive Pulmonary Disease (COPD), Cancer, Solid Organ Transplantation (SOT), Smoking, Cerebrovascular Diseases (Stroke, Encephalopathy), Smoking, Asthma, Chronic Kidney Disease (CKD), Dyslipidemia (DLP), and Heart Diseases (Arrhythmias, Heart Failure or Ischemic Heart Disease), days of onset of symptoms and admission on oxygen use.

To evaluate the impact of complications, the following variables have been studied: respiratory failure with need of mechanical ventilation (MV), Acute Kidney Failure (AKF) dialysis-requiring, deep vein thrombosis (DVT) and/or or Pulmonary Thromboembolism (PTE), Bloodstream Infections (BSI), Pneumothorax, Bacterial Pneumonia, Acute Arrhythmia and Cerebral Ischemia).

The laboratory variables were the Partial Pressure of Carbon dioxide, Inspired Oxygen Fraction (FiO2), Blood Pressure of Oxygen, as well as the Blood Pressure Oxygen / Inspired Oxygen Fraction (P/F Ratio), hemoglobin count, leukocytes, lymphocytes, platelets, INR (international normalized ratio) value, Prothrombin Activity Time, Activated Partial Thromboplastin Time, C-Reactive Protein, D-dimer, Ferritin, Lactate Dehydrogenase and initial impairment on Chest Tomography (assessed by percentage of peripheral ground glass opacity in the total lung area).

3 Results

The present study analyzed data from n=163 patients (64 deaths and 99 discharges) in order to identify clinical and laboratory parameters that are associated with patient survival, considering the length of stay in the ICU.

Initially, tables 1, 2 and 3 present the bivariate analysis to identify the qualitative factors that are significantly associated (p-value <0.05) with the death of patients.

Table 1 lists the variables related to the patient's profile and previous comorbidities. In this table, the following qualitative variables had p-value <0.05: HBP, DM, COPD, Heart Disease, Cerebrovascular Disease.

Table 1 Comorbidities associated with mortality of patients hospitalized in the ICU, with COVID-19, at Hospital Meridional de Cariacica-ES, year 2020

	Total (n=163)	**%**	**Death (n=64)**	**%**	**Discharge (n=99)**	**%**	**p-value**
Sex							0.1697
Masculino	101	62.0	35	34,7	66	65,3	
Feminino	62	38.0	29	46,8	33	53,2	
HBP							0.0060*
Yes	97	59.5	47	48,5	50	51,5	
No	66	40.5	17	25,8	49	74,2	
DM							0.0071*
Yes	48	29.4	27	56.3	21	43.8	
No	115	70.6	37	32.2	78	67.8	
Smoking							0.9723
Yes	24	14.7	10	41.7	14	58.3	
No	139	85.3	54	38.8	85	61.2	
COPD							0.0010*
Yes	18	11.0	14	77.8	4	22.2	
No	145	89.0	50	34.5	95	65.5	
Asthma							0.2929
Yes	10	6.1	6	60.0	4	40.0	

No	153	93.9	58	37.9	95	62.1	
CKD							0.2929
Yes	10	6.1	6	60.0	4	40.0	
No	153	93.9	58	37.9	95	62.1	
Heart Disease							0.0225*
Yes	22	13.5	14	63.6	8	36.4	
No	141	86.5	50	35.5	91	64.5	
Cancer							0.6666
Yes	5	3.1	1	20.0	4	80.0	
No	158	96.9	63	39.9	95	60.1	
SOT							0.7007
Yes	3	1.8	2	66.7	1	33.3	
No	160	98.2	62	38.8	98	61.3	
Obesity							0.4955
Yes	39	23.9	13	33,3	26	66,7	
No	124	76.1	51	41,1	73	58,9	
DLP							0.6733
Yes	16	9.8	5	31,3	11	68,8	
No	147	90.2	59	40,1	88	59,9	
Cerebrovascular Disease							0.0022*
Yes	10	6,1	9	90,0	1	10,0	
No	153	93,9	55	35,9	98	64,1	

*Chi-square test. High Blood Pressure (HBP), Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), Cancer, Solid Organ Transplantation (SOT), Chronic Kidney Disease (CKD), Dyslipidemia (DLP).

In Table 2, which lists laboratory and imaging findings, the following qualitative variables had p-values < 0.05: AKI, anemia and thrombocytopenia.

Table 2 Laboratory and imaging associated with mortality of patients hospitalized in the ICU, with COVID-19, at Hospital Meridional de Cariacica-ES, year 2020

	Total (n=163)	**%**	**Death (n=64)**	**%**	**Discharge (n=99)**	**%**	**p-value**
% GGO							0.4984
<25%	31	19.0	11	35.5	20	64.5	
>25 a 50%	46	28.2	13	28.3	33	71.7	
>50 a 75%	63	38.7	29	46.0	34	54.0	
>75%	23	14.1	11	47.8	12	52.2	
AKI							0.0001*
Yes	27	16.6	20	74.1	7	25.9	
No	136	83.4	44	32.4	92	67.6	
Anemia							<0.0001*

Yes	55	33.7	36	65.5	19	34.5	
No	108	66.3	28	25.9	80	74.1	
Leukocytosis							0.6098
Yes	51	31.3	22	43.1	29	56.9	
No	112	68.7	42	37.5	70	62.5	
Lymphopenia							0.9079
Yes	152	93.3	59	38.8	93	61.2	
No	11	6.7	5	45.5	6	54.5	
Thrombocytopenia							0.0029*
Yes	27	16.6	18	66.7	9	33.3	
No	136	83.4	46	33.8	90	66.2	
Coagulopathy							0.0216
Yes	20	12.3	8	40.0	12	60.0	
No	143	87.7	56	39.2	87	60.8	
Hypercapnia							0.3715
Yes	15	9.2	8	53.3	7	46.7	
No	148	90.8	56	37.8	92	62.2	
Hypoxemia							0.8772
Yes	84	51.5	32	38.1	52	61.9	
No	79	48.5	32	40.5	47	59.5	

*Chi-square test. Acute Kidney Injury (AKI), Ground Glass Opacity (GGO).

Table 3 lists complications and the need for supportive measures with oxygen therapy. In this table, the following qualitative variables had p-value < 0.05: mechanical ventilation, bloodstream infection, acute renal failure, bacterial pneumonia, post-covid arrhythmia and use of supplemental oxygen at admission.

Table 3 Complications associated with mortality of patients hospitalized in the ICU, with COVID-19, at Hospital Meridional de Cariacica-ES, year 2020

	Total (n=163)	**%**	**Death (n=64)**	**%**	**Discharge(n=99)**	**%**	**p-value**
MV							<0.0001*
Yes	80	49.1	60	75.0	20	25.0	
No	83	50.9	4	4.8	79	95.2	
MV>14 days							<0.0001*
Yes	45	27.6	34	75.6	11	24.4	
No	118	72.4	30	25.4	88	74.6	
BSI							0.0444*
Yes	13	8.0	9	69.2	4	30.8	
No	150	92.0	55	36.7	95	63.3	
AKF - dialysis							<0.0001*
Yes	32	19.6	27	84.4	5	15.6	

No	131	80.4	37	28.2	94	71.8	
DVT/PTE							0.7757
Yes	10	6.1	3	30.0	7	70.0	
No	153	93.9	61	39.9	92	60.1	
Pneumothorax							0.1658
Yes	7	4.3	5	71.4	2	28.6	
No	156	95.7	59	37.8	97	62.2	
Bacterial Pneumonia							<0.0001*
Yes	119	73.0	61	51.3	58	48.7	
No	44	27.0	3	6.8	41	93.2	
Post COVID-19 Arrhythmia							0.0372*
Yes	9	5.5	7	77.8	2	22.2	
No	154	94.5	57	37.0	97	63.0	
Oxygen intake							0.0044*
Yes	145	89.0	63	43.4	82	56.6	
No	18	11.0	1	5.6	17	94.4	

*Chi-square test. Mechanical Ventilation (MV), Bloodstream infection (BSI), AKF (Acute Kidney Failure), Deep Venous Thrombosis (DVT), Pulmonary Thromboembolism (PTE).

Table 4 Summary of the risk of mortality of patients hospitalized in the ICU, with COVID-19, at Hospital Meridional de Cariacica-ES, year 2020

	Odds Ratio	**CI95%**		**p-value**
Mechanical Ventilation	59.2500	19.2	182.4	<0.0001*
MV>14 days	9.0667	4.08	20.1	<0.0001*
High Blood Pressure	2.7094	1.37	5.35	0.0060*
Diabetes Mellitus	2.7104	1.35	5.41	0.0071*
COPD	6.6500	2.07	21.2	0.0010*
Heart Disease	3.1850	1.25	8.11	0.0225*
Cerebrovascular Disease	16.0364	1.97	129.9	0.0022*
Oxygen intake	13.0610	1.69	100.7	0.0044*
AKF - dyalisis	13.7189	4.91	38.3	<0.0001*
Bacterial Pneumonia	14.3736	4.21	48.9	<0.0001*
Post COVID-19 Arrhythmia	5.9561	1.19	29.6	0.0372*
BSI	3.8864	1.14	13.2	0.0444*
AKI	5.9740	2.35	15.1	0.0001*
Anemia	5.4135	2.68	10.9	<0.0001*
Plaquetopenia	3.9130	1.63	9.39	0.0029*

* Chi-square test. Mechanical Ventilation (MV), Chronic Obstructive Pulmonary Disease (COPD), AKF (Acute Kidney Failure), AKI (Acute Kidney Injury), Bloodstream Infection (BSI).

For the assessment of the Odds Ratio and Confidence Interval in Tables 1, 2 and 3, the Table 4 shows the Odds Ratio and Confidence Interval. The variables with perceived p-values, in the previous tables, present Odds Ratio >1, which denotes a risk factor for mortality in the bivariate analysis.

The values in table 4 show that the variables associated with the death outcome were mechanical ventilation (OR: 59.25, 95%CI: 19.2-182.4, p<0.0001), MV > 14 days (OR: 9.06, 95%CI: 4.08- 20.1, p<0.0001), high blood pressure (OR: 2.70, 95% CI: 1.37-5.35, p=0.0060), diabetes mellitus (OR: 2.71, 95% CI: 1.35-5.35, p=0.0071), heart disease (OR: 3.18, 95%CI: 1.25-8.11, p=0.0225), cerebrovascular disease (OR: 16.03, 95%CI: 1.97-129.9, p=0.0022), use of supplemental oxygen (OR: 13.06, 95%CI: 1.69-100 , p=0.0044), acute renal failure dialysis-requiring (OR: 13.71, 95% CI: 4.91-38.3, p<0.0001), secondary pneumonia (OR: 13.37, 95% CI: 4.21-48.9, p<0.0001), post-COVID-19 acute arrhythmia (OR: 5.95, 95% CI: 1.19-29.6, p=0.0372), bloodstream infection (OR: 3.88, 95% CI: 1.14-13.2, p=0.0444), acute kidney injury (OR: : 5.97, IC95%: 2.35-15.1, p=0.0001), anemia (OR: 5.41, IC95%: 2.68-10.9, p<0.0001) and thrombocytopenia (OR: 3.91, IC95%: 1.63-9.39, p= 0.0029).

3.1 Multivariate Analysis – Cox Survival Hazard

The variables that obtained p-value <0.05, in the bivariate analysis, were submitted to the multivariate model of survival Cox Survival Hazard. The Proportional Risk Survival Model was performed with n=163 patients, with 64 deaths and 99 survivors. The multivariate model had x2= 66.1 with GL = 21 (degrees of freedom), p-value <0.0001* (highly significant) and -2 Log Likelihood = 475.6.

Figure 1 presents the evaluation according to the analysis model described above, distinguishing deaths from discharges in patients with Anemia admitted to the ICU, using the Kaplan-Meyer diagram.

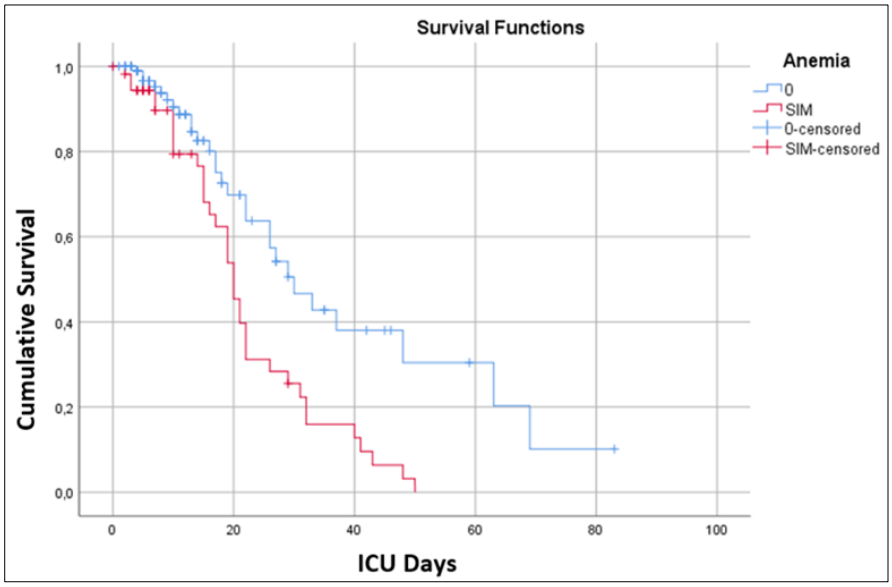

Figure 1 Kaplan-Meyer Diagram of Survival Function of n= 163 patients, being Deaths (n=64) and Survivors (n=99), based on ICU Time (days) according to the presence of Anemia

Figure 2 presents the assessment according to the analysis model described above, distinguishing deaths from discharges in patients undergoing mechanical ventilation admitted to the ICU, using the Kaplan-Meyer diagram.

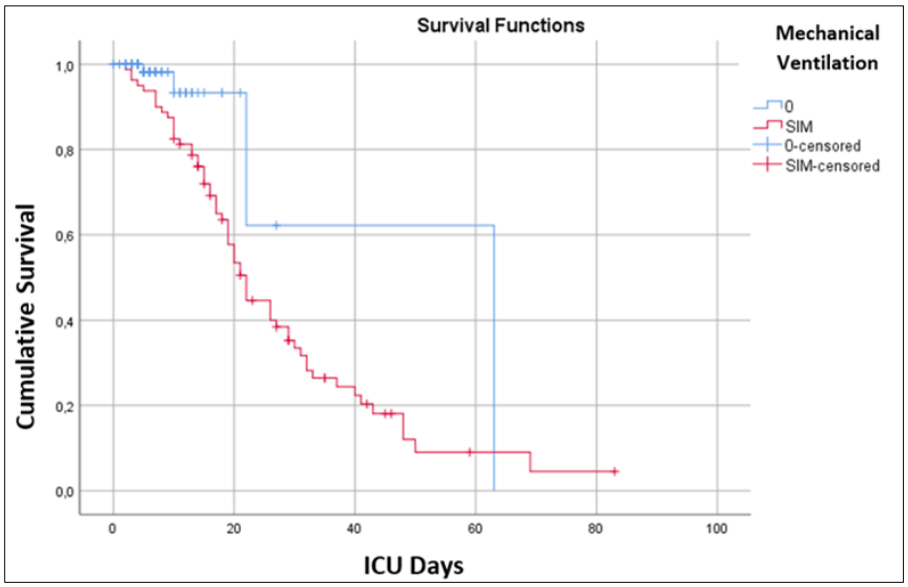

Figure 2 Kaplan-Meyer Diagram of Survival Function of n= 163 patients, being Deaths (n=64) and Survivors (n=99), based on ICU Time (days) according to the performance of Mechanical Ventilation

4 Discussion

4.1 Anemia

This research identified that Anemia on admission is an independent risk factor for mortality in patients hospitalized with COVID-19 in an intensive care setting. In the multivariate analysis, there was statistical significance with p=0.016 (OR=2.17, 95% CI 1.15- 4.09). In a recent meta-analysis, it was identified that the pooled analysis of data showed a significant association of severe disease with anemia.[10] Another study comparing patients with and without anemia showed that anemia on admission is an independent variable for greater severity of COVID-19, in agreement with the result of this study.[11]

4.2 Ferritin

Ferritin is a well-established inflammatory marker in COVID-19, but because it is elevated by several other factors and comorbidities, it cannot be used specifically for patients with COVID-19. In a recent meta-analysis, the importance of ferritin in determining the severity of hospitalized patients was studied, with higher rates being identified in patients with positive COVID-19 when compared to those with a negative test for COVID, there are higher rates of ferritin in more severe patients compared to those with mild to moderate diseases, there are higher ferritin rates in patients who required ICU and in those undergoing orotracheal intubation, and there was also a positive correlation of higher ferritin rates in patients who died compared to those who survived. [12]

Despite being considered an independent marker of severity for COVID-19, in this research there was no statistical significance, with p=0.7759. Only 28 patients (17%) of those studied did not have ferritin data in the electronic chart.

4.3 C-reactive protein

The increase in C-reactive protein, similar to ferritin, can be caused by several factors that lead to the activation of the inflammatory response. C-reactive protein is the most predominant inflammatory acute phase protein, being widely used in the diagnosis of inflammation. In COVID-19, the increase in this inflammatory marker is usually relevant, especially in more severe cases.[13,14] Despite these data, in this work there was no statistical significance in this variable, with p=0.1966.

4.4 Coagulopathies and D-dimer

The prothrombotic state in patients with systemic inflammation causes a greater possibility of developing coagulopathies. COVID-19 coagulopathy is characterized by mild thrombocytopenia, prolonged prothrombin time, and high levels of D-dimer.[15] This research identified that high D-dimer is a risk factor for death, with p=0.0187 and an

estimated cut-off point of 1176, considering that for values above this number there is a sensitivity of 55% and specificity of 58% for identification of patient who died. However, it was not possible to identify by statistical methods the relationship between coagulopathy (assessed by laboratory methods) and increased risk of mortality. Only 13 patients (8%) had no D-dimer laboratory data and only 10 (6%) had no clotting factor data.

Elevated D-dimer was associated with a higher risk of poor outcome in previous researches,[5,16] corroborated by the findings of a meta-analysis that identified that hospital admission with higher D-dimer values is correlated with greater disease severity and higher mortality.[17]

4.5 Lymphopenia and Thrombocytopenia

Marked lymphopenia is a common feature of patients with COVID-19 infection, similar to SARS-CoV-1 and Mers-Cov infection. It was evidenced in a meta-analysis that lymphopenia is an independent variable for the risk of unfavorable evolution.[16] In this research, there was no statistical difference between the patients who were discharged and those who died, with p=0.9079.

In this study it was identified that thrombocytopenia is a risk factor for mortality, with p=0.0029, but in the multivariate analysis it was not possible to identify it as an independent factor. A study carried out at the beginning of the pandemic did not identify thrombocytopenia as a risk factor,[18] while a recent study states that patients with COVID-19 have mild thrombocytopenia and appear to have increased platelet consumption.[5] Despite thrombocytopenia, patients with COVID-19 usually present a hypercoagulative state, which predominates clinically, with thrombosis being much more common than bleeding in these patients.[19]

4.6 Lactate Dehydrogenase

Lactate dehydrogenase is a protein that increases in whole blood as inflammation occurs leading to erythrocyte hemolysis. The increase in lactic dehydrogenase was used to classify severity in some studies, with higher values indicating greater severity of clinical conditions, with greater probability of ICU admission.[18,20,21] In this study, in the bivariate analysis, the LDH dosage was also shown to be a risk factor for increased mortality from COVID-19, with a median of 364.5 IU/L and a cutoff point for deaths of 277 IU/L. However, it is worth mentioning that only 66% of the patients had this exam in their medical records.

4.7 High Blood Pressure and Diabetes Mellitus

There is a positive correlation between hypertension and more severe cases of COVID, perhaps due to direct changes related to affinity with ACE2 or due to cardiovascular changes caused by high blood pressure.[22] Previously published review article shows that arterial hypertension is correlated with more severe cases with an unfavorable outcome for rates of mechanical ventilation and death.[2] Another study shows that both high blood pressure and diabetes were risk factors for ICU admission.[13] Research carried out in the United States identified that Diabetes Mellitus was an independent risk factor for ICU admission and mortality.[23]

This study identified that Hypertension and Diabetes Mellitus are risk factors with p=0.006 and 0.0071 respectively, but in the multivariate analysis it was not possible to establish them as independent risk factors.

4.8 Age and Sex

There is a positive correlation between age and COVID-19 mortality. Increasing age is a risk factor for the disease, with more severe diseases occurring in patients of older age groups. [24,25]

This study identified that age is a risk factor for mortality, with p=0.0027, with a cut-off point of 60 years, with a sensitivity of 58% and specificity of 56% at this cut-off point, coinciding with a study carried out in Brazil.[26]

A recent study indicates that male gender is a risk factor for ICU admission, but it was not associated with mortality.[23] similarly, this work failed to identify a relationship between sex and mortality, with p=0.1697 and confidence interval crossing zero.

4.9 Obesity, Dyslipidemia and Heart Disease

Among the risk factors for serious disease, obesity stands out for having increased its frequency in recent decades, especially in younger patients, exposing an earlier age group to the risks of the disease. It is characterized by being a

disease that indicates unbalanced metabolic health leads to reduced immune system response, chronic inflammation and is related to greater severity of viral disease in patients with COVID-19.[16,27]

Heart disease, which in this study encompasses heart failure, ischemic heart disease and arrhythmias, was identified as a risk factor, with OR: 3.18, 95% CI: 1.25-8.11, p=0.0225. A study carried out in Italy identified similar findings, with higher mortality in this group of patients.[28]

Patients with cardiovascular disease tend to be older, with prevalence increasing with increasing age.[29] The immune system of these patients is more fragile, therefore, they become a population at increased risk for diseases in general, including infectious diseases. [30]

4.10 Complications on ICU

Complications of patients admitted to the ICU tend to occur with the most severe patients, regardless of the reason that led them to be admitted to the intensive care unit. The analysis of these complications can help to identify cases with greater association with mortality and lead to an early approach, enabling better patient care.

4.11 Mechanical Ventilation

Mechanical ventilation is the factor most related to mortality. Obviously, the use of mechanical ventilation is not the reason for the death of these patients. But it is observed that patients who need ventilation have much higher mortality than those who do not. A meta-analysis evaluating the mortality rate in patients on mechanical ventilation identified that approximately half of patients on mechanical ventilation died, ranging from 47.9% (95% CI 46.4-49.4) in patients aged ≤40 years to 84.4% (95% CI 83.3 -85.4%) in patients aged >80 years.[31]

In this study, mechanical ventilation was considered an independent risk factor for death after multiparametric analysis in ICU patients, with OR:17.25 (95%CI: 4.35-68.4 and p-value:<0.0001).

4.12 Deep venous thrombosis and pulmonary thromboembolism

It is known that systemic inflammation, abnormal coagulation status and multiple organ dysfunction are all contributing factors to venous thromboembolism. [32]

However, this study did not identify a higher risk of death related to DVT and PTE, probably due to the low rate of patients in the sample with a radiological diagnosis of thrombosis (n=11). Some patients were treated with full anticoagulation in clinical suspicion, due to the severity and urgency of the condition, not having clinical conditions for transport for angiotomography. Therefore, it was decided not to include these patients in the study, which could be a confounding factor.

4.13 Bacterial Pneumonia

In this study, there was a correlation between secondary pneumonia and mortality with OR: 13.37, 95%CI: 4.21-48.9, p<0.0001. Bacterial pneumonia can occur with the initial phase of viral pneumonia, but more commonly it starts after a few days, and may even occur in the recovery phase. The recognition of secondary pneumonia depends on a high rate of suspicion, since the symptoms of viral and bacterial pneumonia can be very similar and the limitation of repetitive collection of more invasive exams in the respiratory tree, in order to preserve the health of health professionals, makes it difficult further accurate diagnosis of infection overlap. [33,34]

4.14 Acute Renal Failure dialysis-requiring

Dialysis-requiring ARF is a frequent treatment therapy in hospitalized patients, who mainly present with septic shock. However, the virus can cause direct kidney damage, in addition to the problems associated with low blood volume to kidneys. This study identified a higher risk of death in patients who had dialysis-requiring ARF with OR 13.71, CI95% 4.91-38.3 and p<0.0001.

A study carried out to identify survival and chronic kidney disease after COVID, identified that in hospitalized patients requiring dialysis, there was an increase in the risk ratio by 11.3 [CI95%: 9.6-13.1]. [35]

4.15 Post COVID-19 Arrhythmia

Arrhythmia can occur in the context of the most critically ill patients admitted to the ICU, but it appears to be even more common in critically ill patients with COVID-19. Conduction alterations can occur due to hypoxia, inflammatory stress and abnormal metabolism. [36]

This study identified that post COVID-19 arrhythmias were a factor associated with death, with OR: 5.95, 95%CI: 1.19-29.6, p=0.0372. These data are in agreement with findings in other studies, which identified higher mortality in patients who developed this complication. Cardiac arrhythmias can be a direct consequence of the effects of COVID-19 but also secondary to the systemic deleterious effects and interaction with drugs used to treat the disease. [37]

4.16 Study limitations

As this is a retrospective study, there may be flaws both due to lack of data and incorrect recording of data in medical records, especially in the context of pandemic peak. In addition, the retrospective study has a high probability of incurring a selection bias, especially when trying to correlate the causes with the outcome, since it is not possible to say with absolute certainty that the patient's other comorbidities were not responsible for the death, regardless of the COVID-19 infection.

In this study, there was a failure in the collection of a few laboratory tests in some patients. These flaws were identified and described in the body of this work. In addition, the increase in the flow of admissions of patients with respiratory syndrome also generated a high demand for admissions to the ward, another factor that prolonged the length of stay in the ICU of some patients, because there was simply no room/ward space available.

Another important factor to be reported is the variability of drug and non-drug treatment that occurred over the months with the evolution of understanding and care with the disease, the rational use of mechanical ventilation, better adjustments of ventilation parameters, among others, likely to affect mortality.

5 Conclusion

The identification of predictive factors of mortality in patients with COVID-19 makes it possible to prioritize patients at higher risk of mortality from the disease, instituting earlier treatment to avoid complications that lead to death. This study identified that anemia on admission and the need for mechanical ventilation during ICU admission are independent variables for predicting mortality.

Compliance with ethical standards

Acknowledgments

The participation of Robert Russ for editing the English language of this manuscript is acknowledged

Disclosure of conflict of interest

The authors state there is no conflict of interest.

Statement of ethical approval

The study was approved by the Research Ethics Committee of Universidade Vila Velha (CAAE: 49128821.4.0000.5064), which is subject to the norms of the National Health Council – Ministry of Health of Brazil.

Statement of informed consent

The informed consents were presented to the patient or their legal representative, online, due to the context of the pandemic, participating in the study only those in which there was agreement.

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