DOI: https://doi.org/10.17921/2447-8938.2024v26n4p237-243

A Cross-Sectional Study of Morbidity and Mortality Factors in COVID-19 ICU Patients from the Brazilian Mid-West

Estudo Transversal dos Fatores de Morbidade e Mortalidade em Pacientes com COVID-19 em uma UTI do Centro-Oeste Brasileiro

Joyce Lara de Lima Mendes[a]; Antonio Márcio Teodoro Cordeiro Silva[a]

Pontifícia Universidade Católica. GO, Brazil.
E-mail: joycelaraenf@gmail.com

Abstract

Although the COVID-19 pandemic has officially ended, understanding factors influencing morbidity and mortality among ICU-admitted patients remains essential. This study aimed to investigate morbidity, mortality, and associated factors among SARS-CoV-2 patients admitted to an ICU in the Midwest region of Brazil. This observational, retrospective, cross-sectional study was conducted from March to December 2020, including patients with confirmed COVID-19 via RT-PCR upon ICU admission. Clinical and epidemiological data were extracted from medical records to analyze morbidity and mortality factors. A total of 69 medical records were reviewed, comprising 24 (35%) female and 45 (65%) male patients with a mean age of 58 years (range 30–91). Diabetes mellitus and obesity showed a positive correlation (95%CI=0.435; p=0.072). Factors associated with mortality and prolonged hospital stay included systemic arterial hypertension, chronic obstructive pulmonary disease, obesity, and smoking. Urea plasma levels significantly increased during ICU stay (p<0.001) among patients who did not survive, unlike those discharged. Length of stay correlated with in-hospital mortality (95%CI=0.031–0.479; p=0.002) and with diabetes mellitus (95%CI=0.143–0.572; p=0.025). Regression analysis identified significant associations between in-hospital mortality and elevated urea levels (OR=1.04; 95%CI=1.01–1.07; p=0.0005) and female gender (OR=13.1; 95%CI=1.58–108.85; p=0.017). Therapeutic heparin use was associated with a shorter hospital stay. Comorbidities were linked to extended hospitalization and increased mortality in COVID-19 patients. Elevated urea levels at admission and during ICU stay were strongly associated with in-hospital mortality, especially among female patients.

Keywords: Covid-19. Urea Levels. Comorbidities. Morbidity and Mortality.

Resumo

Embora a pandemia de COVID-19 tenha sido oficialmente declarada encerrada, compreender os fatores que influenciam a morbidade e mortalidade entre pacientes admitidos em UTI permanece essencial. Este estudo teve como objetivo investigar a morbidade, mortalidade e fatores associados entre pacientes com SARS-CoV-2 internados em uma Unidade de Terapia Intensiva (UTI) na região Centro-Oeste do Brasil. Trata-se de um estudo observacional, retrospectivo e transversal realizado entre março e dezembro de 2020, incluindo pacientes com COVID-19 confirmada por RT-PCR na admissão à UTI. Dados clínicos e epidemiológicos foram extraídos de prontuários médicos para análise de fatores de morbidade e mortalidade. Foram revisados 69 prontuários, incluindo 24 (35%) pacientes do sexo feminino e 45 (65%) do sexo masculino, com média de idade de 58 anos (variação de 30–91 anos). Observou-se uma correlação positiva entre diabetes mellitus e obesidade (IC95%=0,435; p=0,072). Os fatores associados à mortalidade e à maior permanência hospitalar incluíram hipertensão arterial sistêmica, doença pulmonar obstrutiva crônica, obesidade e tabagismo. Os níveis plasmáticos de ureia aumentaram significativamente durante a permanência na UTI (p<0,001) entre os pacientes que não sobreviveram, ao contrário daqueles que receberam alta. O tempo de internação mostrou correlação com a mortalidade hospitalar (IC95%=0,031–0,479; p=0,002) e com o diabetes mellitus (IC95%=0,143–0,572; p=0,025). A análise de regressão revelou associações significativas entre mortalidade hospitalar e níveis elevados de ureia (OR=1,04; IC95%=1,01–1,07; p=0,0005), bem como com o sexo feminino (OR=13,1; IC95%=1,58–108,85; p=0,017). O uso terapêutico de heparina foi associado a uma menor permanência hospitalar. Comorbidades foram associadas a hospitalização prolongada e aumento da mortalidade em pacientes com COVID-19. Níveis elevados de ureia na admissão e durante a hospitalização foram fortemente associados à mortalidade hospitalar, especialmente entre pacientes do sexo feminino.

Palavras-chave: Covid-19. Níveis de Ureia. Comorbidades. Morbidade e Mortalidade.

1 Introduction

The first cases of COVID-19 were reported at the end of December 2019 in Wuhan, China, and the disease culminated in a pandemic within weeks. As of September 30, 2020, more than 33 million cases have been recorded worldwide, with more than 1 million deaths[1]. In Brazil, death tolls reached

a peak of 4,148 daily deaths in April 2021[2]. As population continuously got recommended shots of vaccine, death rates slowly started to decline and by February 2022, more than 300 million doses of vaccine had been delivered to the population only in Brazil[2].

From the natural history of COVID-19, it is possible to identify three phases of the disease. The first phase corresponds to the onset of the disease and is characterized by the development of mild to moderate influenza-like symptoms[3,4]. At this stage, the virus can be detected by molecular analysis via reverse transcriptase-polymerase chain reaction (RT-PCR) and most patients can be asymptomatic and transmissible. In some cases, anosmia or ageusia may be the only presenting symptom in approximately 3% of individuals with COVID-19[5].

Covid-19's most common symptoms in hospitalized patients include fever (70-90%), dry cough (60-86%), dyspnea (53-80%), fatigue (38%), myalgias (15-44%), nausea/vomiting or diarrhea (15-39%), headache (25%) and rhinorrhea (7%)[5]. Recurrent laboratory changes among hospitalized patients include lymphopenia (83%), elevated inflammatory markers, e.g. erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-α, IL-1, IL-6 and abnormal coagulation parameters, e.g. prolonged prothrombin time, thrombocytopenia, elevated D-dimer and low fibrinogen[6]. Common radiographic findings of patients with COVID-19 include bilateral infiltrates predominantly in the lower lobe on chest X-ray imaging and bilateral and peripheral lower lobe ground-glass opacities and/or consolidation on chest CT[1].

The immune response modifies the clinical course of COVID-19. A relevant feature of the disease is the episode, in 10-20% of patients of a sudden clinical worsening 7-10 days after the onset of symptoms, increasing the risk of acute respiratory failure (ARF), organ failure and death. In a second stage, known as the pulmonary phase, it is possible to detect symptoms like those of pneumonia, in addition to imaging parameters such as pulmonary opacities seen on chest X-rays and/or opacities with a ground-glass appearance on computed tomography (CT) scans[7]. Regarding laboratory parameters, T and B cell lymphopenia, neutrophilia and a reduction in eosinophils and monocytes are observed[8,9], and these results are predictive of the clinical severity of the infection.

Pneumonia caused by COVID-19 has particularly distinctive characteristics, such as severe hypoxemia, often associated with altered pulmonary compliance of varying degrees of severity, which can lead to the need for intubation and artificial ventilation. This corresponds to a typical stage-3 disease which is characterized by hyperinflammation and pulmonary sepsis, which can aggravate the prognosis and lead to death[10].

The most frequent complications among patients hospitalized with COVID-19 are pneumonia (75%), ARDS (15%), acute liver injury, cardiac injury, including troponin elevation (7-17%), acute heart failure, arrhythmias and myocarditis; pro-thrombotic coagulopathy resulting in venous and arterial thromboembolic events (10-25%), neurological manifestations, including impaired consciousness (8%), acute cerebrovascular disease (3%) and shock (6%)[11,12]. Rare complications among critically ill patients with COVID-19 include "cytokine storm" and macrophage activation syndrome, i.e. secondary hemophagocytic lymphohistiocytosis[1].

In the infection caused by SARS-CoV-2, hypercoagulability plays an important role in its pathophysiology, and is intrinsically related to the inflammatory condition in a cross-interaction: inflammation induces the activation of coagulation, and this, in turn, accentuates inflammatory activity[13].

Although the number of severe cases of COVID-19 has drastically decreased with the vaccines, still some patients need hospital support[14-16]. More recently, the guidelines for severe COVID-19 treatment include administration of dexamethasone or other systemic corticoids and prophylactic doses of heparin. Treatment can also include immunomodulators and Remdesivir depending on how critical the patient is (NIH Guidelines for COVID-19 treatment, 2023). Therefore, the aim of the present study is to look at the factors associated morbidity and mortality in patients admitted to an ICU in Brazil during the pandemic in 2020.

2. Material and Method

2.1 Study Design

This is a retrospective, observational, cross-sectional study, analyzing medical records, in which the population consisted of patients assisted in an ICU in the Midwest of Brazil. The approach was quantitative, designed to examine the relationships between the selected variables[17].

2.2 Ethical Aspects

This study was approved by the Research Ethics Committee of the University of Rio Verde (number 4.563.056). The number of the Certificate of Submission for Ethical Consideration (CAAE) on the *Plataforma Brasil* is 43454621.2.0000.5077. The names of the research participants have been kept completely confidential. All the information was taken from their medical records, laboratory tests and clinical evolution. This study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure rigorous and transparent reporting of the research methodology and findings.

2.3 Participants

This study was carried out in the ICU of Santa Terezinha Hospital in the Midwest region of Brazil. It is a private institution, with a type II level of complexity, with 9 beds dedicated to the care of adult clients with part of the ICU beds (4 beds) exclusively dedicated to the care and treatment of COVID-19. The medical records selected belong to patients

admitted between March 24 and December 31, 2020, of both sexes. During this period, 74 patients were admitted to the ICU with a COVID-19 diagnosis. All medical records of patients aged 18 and over, male or female, with clinical and laboratory criteria for COVID-19 infection were included.

Records with inaccurate or incomplete information and records in which the cause of death was not clearly determined to be Sars-CoV-2 infection were excluded. Four medical records were not included for analysis because they were being audited by health insurance companies and one medical record was not included because the client was hospitalized after December 31, 2020.

2.4 Exposure measurements and variables

In order to evaluate the clinical and epidemiological data of this study, the date of the tests, age and gender of the patient, time of hospital stay, and in-hospital death were recorded. Moreover, the following comorbidities were recorded: systemic arterial hypertension (SH), chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), obesity, diabetes mellitus (DM) and smoking. Laboratory test results were also considered, including arterial blood gas: PH, PO2, PCO2, bicarbonate; prothrombin activity time (PAT)/international normalized ratio (INR), activated partial thromboplastin time (APTT)/(sec), lactate, urea, creatinine and D-dimer. Finally, indications for hemodialysis and/or treatment with methylprednisolone, dexamethasone or heparin therapy were noted.

2.5 Statistical Analysis

Due to the type of data analysis, individual mode, without follow-up, an expected prevalence (or proportion) of 75% was used in the sample calculation, with a margin of error of 6.0% and a 95% confidence interval. Thus, the sample size required for this analysis (prevalence calculation) was 65 patients.

All statistical analyses were carried out using Microsoft Office Excel 2019, PASS 11 (sample size calculation), MINITAB 19 or GraphPad Prism 10. Confidence intervals were constructed for the proportions for each category, contingency tables to establish conditions that promote increased risk for the pathologies under study and descriptive statistics. Parametric data were analyzed with paired t-test and non-parametrical data were analyzed using Wilcoxon matched-pairs. Two or more groups of data were analyzed with One-Way ANOVA with Dunnett's as post-test.

Spearman's correlation coefficient was used to analyze the intensity and direction of the monotonic relationship between two continuous or ordinal variables. It is known that in a monotonic relationship, the variables tend to move in the same relative direction, but not necessarily at a constant rate. To calculate the Spearman correlation, Minitab assigns ranks to the raw data. The Minitab program then calculated the correlation coefficient with the data assigned ranks. Furthermore, we used logistic regression analysis that seeks to assess the existence and degree of statistical dependence between random variables, i.e. those that have a probability distribution. A significance level of 0.05 was considered in all analyses.

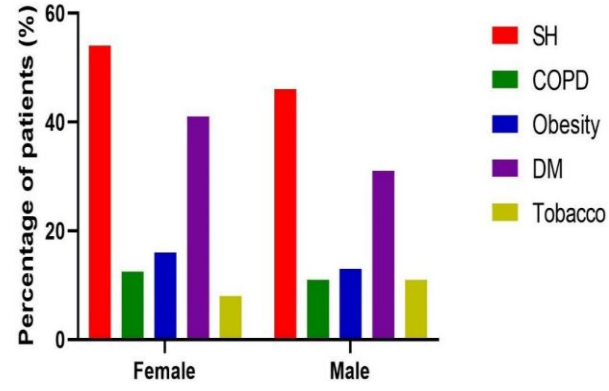
Spearman's correlation coefficient was used to analyze the intensity and direction of the monotonic relationship between two continuous or ordinal variables. It is known that in a monotonic relationship, the variables tend to move in the same relative direction, but not necessarily at a constant rate. To calculate the Spearman correlation, Minitab assigns ranks to the raw data. The Minitab program then calculated the correlation coefficient with the data assigned ranks. Furthermore, we used logistic regression analysis that seeks to assess the existence and degree of statistical dependence between random variables, i.e. those that have a probability distribution. A significance level of 0.05 was considered in all analyses.

3 Results and Discussion

3.1 Patients demographics and comorbidities

A total of 69 medical records were analyzed, of which 24 (35%) were female and 45 (65%) males, with an average age of 58.5 (min: 30, max: 91) years. Regarding the comorbidity variables analyzed, the medical records showed that 34 (49%) patients had SH, 8 (12%) had COPD, 24 (35%) had a previous diagnosis of DM and 10 (14.5%) were obese. None of the participants had a previous diagnosis of CVD, while 7 (10%) were smokers. Figure 1 shows the detailed frequency of these comorbidities in relation to gender.

Figure 1 - Comorbidities per gender. Representation of percentage of patients in female and male groups (N= 24 and 45, respectively). SH, systemic hypertension; COPD, chronic obstructive pulmonary disease; and DM, diabetes mellitus

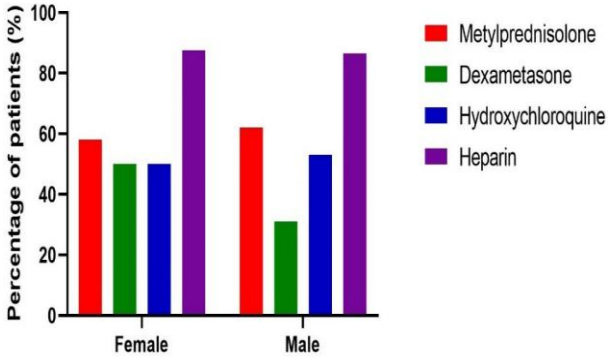


Source: the authors.

Regarding hospitalization variables, 17 patients (25%) required hemodialysis and 21 patients (30.5%) died. With regard to the medications used, 42 patients (61%) were given methylprednisolone, 26 patients (38%) were given dexamethasone, 36 patients (52%) were prescribed with

hydroxychloroquine and 60 patients (89%) were given heparin in therapeutic doses. Figure 2 shows the detailed percentage of patients prescribed with these drugs in relation to gender.

Figure 2 - Medications per gender. Representation of percentage of patients in female and male groups (N= 24 and 45, respectively) prescribed with each medication



Source: the authors

Next, we investigated if gender, age, comorbidities, or medications interfered in time spent in the IUC or in the in-hospital death. We found a positive correlation between age and in-hospital death (95% CI: 0.01; 0.469, p= 0.038), but not between age and time spent in the ICU (95% CI: -0. 13; 0.33, p= 0.39). Gender in turn did not correlate with any other variable.

Regarding comorbidities, we only found a statistically significant positive correlation between DM and time spent in the ICU (95% CI: 0.03; 0.479, p= 0.025). For all other comorbidities, our results show no correlation between variables. According to the WHO, by January 2024, 774 million people were reported with Covid-19 worldwide. It is estimated that the pandemic killed 7 million people and imposed a huge burden in healthcare systems all over the world[18].

Several studies have identified the following variables as prognostic factors for COVID-19-related mortality: age, gender (male), obesity, cardiovascular disease, diabetes, hypertension, dyslipidemia, COPD, smoking, neoplasia, cerebrovascular disease, dementia and chronic kidney disease[19]. Furthermore, patients who need ICU care are the most vulnerable targets for death in COVID-19 with up to 61.5% mortality in patients that require mechanical ventilation[20,21].

Patients with diabetes are at significantly increased risk of developing serious infections and impaired lung function. In addition, there are also unique and complex interactions between antidiabetic drugs and other agents commonly used for DM-related co-morbidities with Covid-19 infection. The coexistence of diabetes and obesity or "diabesity" is characterized by a pro-inflammatory state, driven by cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha[22]. Our data identified a correlation between DM and obesity, indicating impaired recovery in patients infected with the virus when they have DM, which can be found in the correlation between obesity and obesity.

DM is associated with immune dysfunction, increased susceptibility to inflammation and reduced viral clearance. In addition, a possible association between SARS-CoV-2 and the renin-angiotensin-aldosterone system may increase the risk of DM. Adhesion of SARS-CoV-2 to target cells and may worsen the severity of COVID-19[23]. SARS-CoV-2 has glycoprotein receptors on its surface, which bind to ACE2 receptors on target cells. Upon binding to ACE2, the virus is processed by proteases such as transmembrane serine protease 2 and furin, resulting in the internalization of the virus complex. ACE and furin expression are increased in DM, which may facilitate viral entry and replication[24].

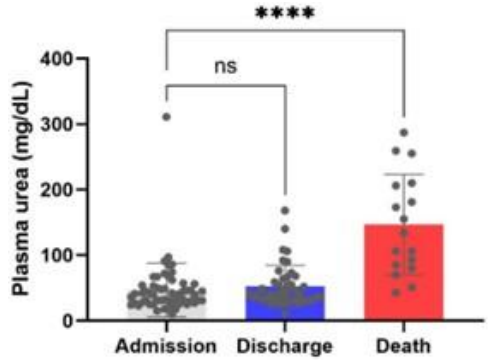
Our data show that the more time patients spent in the ICU, the more likely they were to die in the hospital (95% CI: 0.14; 0.57, p= 0.002). A cohort study obtained data for 3,927 COVID-19 positive patients from six independent centers comprising 33 different hospitals. Demographic, clinical and laboratory variables were collected at hospital admission. The COVID-19 Mortality Risk (CMR) tool was created to predict mortality. Its discrimination performance was subsequently evaluated in three validation cohorts. The derivation cohort of 3,062 patients had an all-cause mortality rate of 26.84%. Increased age decreased oxygen saturation (≤93%), elevated C-reactive protein levels (≥130 mg/L), blood urea nitrogen (≥18 mg/dL) and blood creatinine (≥1.2 mg/dL) were identified as primary risk factors, validating the clinical findings[26]. In this sense, we similarly found in our patients a correlation of urea plasma levels with mortality although American studies use blood urea nitrogen.

On the other hand, it is inferred that among other factors and direct viral effects, the increase in the vasoconstrictor angiotensin II, the decrease in the vasodilator angiotensin and the sepsis-induced release of cytokines may trigger a coagulopathy in COVID-19 patients. Coagulopathy has been reported in up to 50% of patients with severe manifestations of COVID-19. Limited data suggests a high incidence of deep vein thrombosis and pulmonary embolism in up to 40% of patients, despite the use of a standard dose of low molecular weight heparin (LMWH) in most cases. Prophylactic LMWH has been recommended by the International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (ASH), but the best effective dosage is uncertain[27].

3.2 Clinical Laboratory Measurements

Considering laboratory results, we found that urea levels were significantly higher in patients upon death (p<0.0001), but not upon discharge (p=0.79) (Figure 3).

Figure 3 - Urea levels at admission, discharge and death. Data are described as mean ± SD of plasma concentrations of urea (mg/ml) and were compared using One-Way ANOVA (N= 69). ****p<0.0001; ns, non-significant



Source: the authors

Moreover, we found statistically significant correlations for in-hospital death and urea, as well as length of stay (days) with therapeutic heparin or urea. We observed positive statistically significant correlations between time spent in the ICU and urea levels (p< 0.001), therapeutic use of heparin (p< 0.001) and prescription of hemodialysis (p< 0.001). In-hospital death, on the other hand had a positive correlation with pCO_2 (p= 0.01), but also urea levels (p< 0.001) and prescription of hemodialysis (p< 0.001) (Table 1).

Table 1 - Correlations between in-hospital death or time spent in the ICU and laboratory tests.

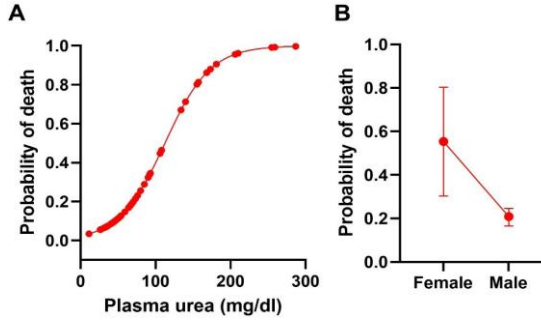
Variable 1	Variable 2	Correlation	95% CI	p-value
In-hospital death	pCO2	0.32	0,070 - 0,532	0.01
	Urea	0.63	0,430 - 0,775	0.000
	Hemodialysis	0.57	0,373 - 0,728	0.000
Time spent in ICU	*Heparin	0.49	0,282 - 0,665	0.000
	Urea	0.51	0,284 - 0,686	0.000
	Hemodialysis	0.55	0,354 - 0,713	0.000

Spearman correlation. *Used in therapeutic dose
Source: the authors.

A prospective cohort study of 701 COVID-19 patients admitted to a tertiary university hospital showed that on admission, 43.9% of patients had proteinuria and hematuria. The prevalence of elevated serum creatinine, elevated blood urea nitrogen and estimated glomerular filtration below 60 ml/min/1.73m2 were 14.4, 13.1 and 13.1%, respectively. During the study period, acute kidney injury occurred in 5.1% of patients. Kaplan-Meier analysis showed that patients with kidney disease had a significantly higher risk of in-hospital death[25]. This is in line with our findings regarding the correlation of urea with in-hospital death and length of hospital stay. In addition to the regression analysis, which showed a significant correlation between urea and female gender.

According to the regression analysis, urea (OR=1.04; 95%CI=1.01-1.07; p=0.0005) and female gender (OR=13.1; 95%CI=1.58-108.85; p=0.017) were correlated to in-hospital death (Figure 4). A binary logistic regression was carried out to see which variables were predictive of patient death. The model pointed that the association of gender and urea plasmatic levels was statistically significant (χ^2=35.82; p<0.001; R2=47.3%).

Figure 4 - Probability of death predicted by binary logistic regression. The graph illustrates the probability of death predicted by a binary logistic regression model. The x-axis represents the independent variables, plasma urea (A) or gender (B), while the y-axis represents the probability of death. A. Each dot represents the death probability of the patient according to the plasmatic urea levels (mg/dl). B. Mean death probability ± SD for each group of patients. Solid lines represent the fit of the regression function



Source: the authors

Finally, the analysis of variance, using the likelihood ratio test, also showed significance within these variables (Table 2).

Table 2 - Analysis of variance results for gender and ureal plasmatic levels on probability of death

Likelihood ratio					
Source	**DF**	**Deviation**	**Mean**	**Chi-squared**	**p-value**
Regression	2	35.8	17.8		
Gender	1	7.7	7.7	35.82	0.000
Urea levels	1	32.75	32.75	7.72	0.005
Error	56	35	0.62	32.7	0.000
Total	58	70.8			

DF – degrees of freedom; $Deviation_{Ad}$ – Adjusted deviation; $Mean_{Ad}$ – Adjusted mean.
Source: the authors

Antiplatelet therapy can be effective in improving the ventilation/perfusion ratio in COVID-19 patients with severe respiratory failure. The effects may be sustained by preventing and interfering with clot formation in pulmonary capillary vessels and by modulating megakaryocyte function and platelet adhesion. Currently, only one retrospective study has demonstrated an advantage of heparin anticoagulant therapy of LMWH in terms of survival in patients with severe COVID-19 and signs of sepsis-induced coagulopathy[28]. In this study, no correlation was found between heparin administration and blood gas parameters or any other laboratory data that influenced the prognosis or improvement of these parameters in the patients in this study. However, we found that the use of a therapeutic dose correlated with the length of hospital stay, probably justifying its interaction with better patient outcomes. Similarly, a retrospective, multicenter cohort study of COVID-19 patients found that higher doses of heparin anticoagulation were associated with lower mortality in these hospitalized patients[29].

In conclusion, data from our patients indicated that some comorbidities interfere with length of hospital stay and increased mortality, such as hypertension, COPD, obesity and DM, as well as smoking. Our findings also emphasize that the prevalence of uremia on admission, in the ICU, and during hospitalization in COVID-19 patients is high and is associated with in-hospital mortality and female gender.

Acknowledgments

Authors thank the UCI service of Santa Terezinha Hospital in Rio Verde, state of Goiás.

References

1. Gautret P, Million M, Jarrot PA, Camoin-Jau L, Colson P, Fenollar F, et al. Natural history of COVID-19 and therapeutic options. Expert Rev Clin Immunol 2020;16(12):1159-84. doi:10.1080/1744666X.2021.1847640.
2. Dos Santos CV, Valiati NC, de Noronha TG, Porto VB, Pacheco AG, Freitas LP, et al. The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: a registry-based study. Lancet Regional Health–Americas 2023;20. doi: 10.1016/j.lana.2023.100465.
3. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, Yuen KY. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Micro Infect 2020;9(1):221-36. doi:10.1080/22221751.2020.1719902
4. Kong WH, Li Y, Peng MW, Kong DG, Yang XB, Wang L, Liu MQ. SARS-CoV-2 detection in patients with influenza-like illness. Nat Microbiol 2020;5(5):675-8. doi:10.1038/s41564-020-0713-1
5. Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5(7):667-78. doi:10.1016/S2468-1253(20)30126-6
6. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. The Lancet Haematology 2020;7(6):e438-40. doi:10.1016/S2352-3026(20)30145-9.
7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
9. Qin C, Ziwei MP, Tao SY, Ke PC, Shang MM. Dysregulation of immune response in patients with COVID-19 in Wuhan. Clin Infect Dis 2020;71(15):762-8. doi:10.1093/cid/ciaa248.
10. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive care medicine 2020;46:1099-102. doi:10.1007/s00134-020-06033-2.
11. Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020;26(6):845-8. doi:10.1038/s41591-020-0897-1.
12. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020;34:101623. doi: 10.1016/j.tmaid.2020.101623.
13. Zhang S, Zhang J, Wang C, Chen X, Zhao X, Jing H, et al. COVID19 and ischemic stroke: Mechanisms of hypercoagulability. Int J Mol Med 2021;47(3):21. doi:10.3892/ijmm.2021.4854
14. Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Giattino C, Hasell J, Macdonald B, et al. (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. https://ourworldindata.org/coronavirus Accessed [1/15/2024];
15. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [1/15/2024]. NIH Guidelines for COVID-19 treatment, 2023
16. Link-Gelles R, Weber ZA, Reese SE, et al. Estimates of bivalent mRNA vaccine durability in preventing COVID-19-associated hospitalization and critical illness among adults with and without immunocompromising conditions—VISION Network, September 2022–April 2023. MMWR Morb Mortal Wkly Rep 2023;72(21):579-588. doi:10.15585/mmwr.mm7221a3
17. Creswell JW. A concise introduction to mixed methods

research. SAGE; 2021.

18. WHO, Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected, World Health Organization, 2020. https://www.who.int/publications/i/item/10665-332299

19. Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One 2020;15(11):e0241955. doi: 10.1371/journal.pone.0241955

20. Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. Hepatol 2020;72(2):389-398. doi: 10.1002/hep.31301.

21. Lavrentieva A, Kaimakamis E, Voutsas V, Bitzani M. An observational study on factors associated with ICU mortality in Covid-19 patients and critical review of the literature. Sci Rep 2023;13:7804. doi:10.1038/s41598-023-34613-x.

22. Chee, Y.J.; Tan, S.K.; Yeoh, E. Dissecting the interaction between COVID-19 and diabetes mellitus. J Diabetes Investig 2020;11(5):1104-14. doi: 10.1111/jdi.13326.

23. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382(17):1653-9. doi: 10.1056/NEJMsr2005760.

24. Fernández A. Targeted Disassembling of SARS-CoV-2 as It Gets Ready for Cell Penetration. ACS Med Chem Lett 2020;11(11):2055-7. doi: 10.1021/acsmedchemlett.0c00548.

25. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020 May 1;97(5):829-38. doi:10.1016/j.kint.2020.03.005

26. Bertsimas D, Lukin G, Mingardi L, Nohadani O, Orfanoudaki A, Stellato B, et al. COVID-19 mortality risk assessment: An international multi-center study. PloS One 2020 Dec 9;15(12): e0243262. doi:10.1371/journal.pone.0243262.

27. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. Clin Appl Thromb Hemost 2020 Jan-Dec;26:1076029620938149. doi:10.1177/1076029620938149.

28. Viecca M, Radovanovic D, Forleo GB, Santus P. Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. Pharmacol Res 2020;158:104950. doi: 10.1016/j.phrs.2020.104950

29. Ionescu F, Jaiyesimi I, Petrescu I, Lawler PR, Castillo E, Munoz-Maldonado Y, et al. Association of anticoagulation dose and survival in hospitalized COVID-19 patients: a retrospective propensity score-weighted analysis. Eur J Haematol 2021;106(2):165-74. doi:10.1111/ejh.13533.