Clinical Characteristics and Risk Factors for Mortality of Hospitalized Patients with Severe COVID-19 in Intensive Care Unit: a retrospective cohort study

ABSTRACT

Objective: To describe the clinical characteristics, complications, and risk factors for mortality ofhospitalized patients with severecoronavirus disease 2019 (COVID-19) during intensive care therapy.

Methods: This single-center retrospective cohort study included 149 patients with severe COVID-19 admitted to an intensive care unit (ICU) from April 2020 to August 2021. Demographic characteristics, medical history, underlying comorbidities, laboratory findings, complications occurring during ICU stay, and mortality were collected and analyzed.Survival and Cox regression analysis were performed to identify risk factors associated with mortality.

Results: Out of 149 patients, 97 (65.1%) were women, and 67 of them were either pregnant or in the early postpartum period. The patients' ages ranged from 16 to 89 years, with a mean (SD) of 44.4 (18.9) years.The need for mechanical ventilation(72.5%) and the development of acute kidney injury (32.9%) were the most frequent complications. Thirty-eight (25.5%) patients died. The subgroup analysis of women showed that being pregnant/postpartum was not associated with a lower frequency of death.However, after adjustment, only increasing age ($p<0.001$)and a high AST-to-ALT ratio($p<0.001$) were independent predictors of death.

Results: Out of 149 patients, 97 (65.1%) were women, and 67 of them were either pregnant or in the early postpartum period. The patients' ages ranged from 16 to 89 years, with a mean (SD) of 44.4 (18.9) years.The need for mechanical ventilation(72.5%) and the development of acute kidney injury (32.9%) were the most frequent complications. Thirty-eight (25.5%) patients died. After adjustment, increasing age ($p<0.001$) and high AST-to-ALT ratio at admission ($p<0.001$) were independent predictors of deathboth in total sample and among women sub-group.High white blood cell count was also associated to death in the total sample analysis.

Conclusion: The most common complications among severe COVID-19 patients in the ICU were the need for mechanical ventilation and acute kidney injury.Increasing age and a high AST-to-ALT ratio at admission were independent predictors of fatality among all patients and even among pregnant/postpartum women.

KEYWORDS:COVID-19, pregnancy, postpartum women, comorbidities, intensive care,mortality.

INTRODUCTION

The disease caused by the 2019 coronavirus (COVID-19) emerged in China and, within a few months, spread globally, resulting in a devastating pandemic.While initially characterized as a flu-like syndrome, COVID-19 can progress to severe forms, often complicated by acute respiratory failure that frequently requires intensive therapy and the use of mechanical ventilation [1].Up to December 2023, over 772 million cases and nearly 7 million deaths from COVID-19 had been documented worldwide. Brazil is the country with the second-highest number of COVID-19 deaths globally, with an accumulated total of 702,116 deaths during that same period [2].

Several studies have demonstrated that older age, heart disease, diabetes mellitus, obesity, cancer, and chronic lung disease are risk factors for higher hospital mortality due to COVID-19. Additionally, laboratory alterations such as leukocytosis, lymphopenia, thrombocytopenia, elevated interleukin 6, elevation of lactate dehydrogenaseand troponin I have also been markers of increased disease severity [3-6].

In addition to viral pneumonia, COVID-19 can lead to acute cardiac or kidney injury (AKI) [7-9]. The incidence of AKI can affect up to 39% of patients admitted to an intensive care unit (ICU), with renal replacement therapy being necessary in approximately 16% of all COVID-19cases [10].Another risk factor for severe COVID-19 is pregnancy and the postpartum period, which are associated with a higher risk of ICU admission, the need for mechanical ventilation, and prematurity [11].

Ecologic study has found significant differences within the territory regarding mortality patterns as a function of geographic location and population composition [12].Detailed data on demographic characteristics, comorbidities, risk factors, and clinical outcomes from community hospitals are needed to fully characterize the spectrum of the COVID-19 and to allow health care providers to prepare tailored interventions for their patients. For that reason, the objective of this study was to describe the clinical characteristicsand risk factors for death of patients with COVID-19 hospitalized in anICUof a public community hospital in the Central Region of Brazil.

PATIENTS AND METHODS

The study was conducted in the ICU of the Júlio Müller University Hospital, which is a medium-sized hospital located in the Central Region of Brazil. This hospital was involved in the local public healthcare service's efforts to provide care for critically ill COVID-19 patients during pandemic. All the patients who were admitted to the ICU of the study hospital between April 2020 and August 2021 were included in this study.Many of these patients were pregnant or in the early postpartum period, as the study hospital is the region's only facility with public neonatal ICU facilities. All patients had their COVID-19 diagnosis confirmed through real-time reverse transcription-polymerase chain reaction, rapid antigen testing for nasopharyngeal specimens, or by testing positive for IgM antibodies against SARS-CoV-2.

Data on age, gender,pregnancy/postpartum status, comorbidities, clinical and laboratory characteristics, as well as clinical outcomes such as the need for mechanical ventilation and occurrences of complications and death during the ICU stay were collected.Incident complications such as acute heart failure, acute renal failure, thromboembolic events, arterial occlusion, acute liver failure, significant bleeding, the need for orotracheal intubation, and death were considered relevant outcomes in this study. The definitions of organ failures followed the guidelines established by major scientific societies, as previously published [13-16].

The study assessed several risk factors for mortality, including the time elapsed between symptom onset and ICU admission, peripheral oxygen saturation (SpO_2), sequential organ failure assessment (SOFA) scoreand mechanical ventilation upon admission, pregnancy/postpartum status, the presence of abnormal laboratory results in the blood count or blood chemistry upon admission, and pre-existing comorbidities.SOFA scores were stratified into less than 2 and 2 or more, as this baseline cutoff is associated with a high risk of death in patients with sepsis[17]. Aspartate (AST) and alanine (ALT) aminotransferases were analyzed using the AST/ALT ratio, which has previously been shown to be a reliable predictor of in-hospital mortality in COVID-19 patients [18].

Since each comorbidity occurred at a low frequency among the study patients, the analysis of this variable as a risk factor was conducted by the combination of arterial hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic pulmonary disease, chronic kidney disease, AIDS, obesity (body mass index (BMI) above 30 kg/m^2), and cancer.The definition of obesity in pregnant and postpartum womenwas based on the standardized BMI adequacy table for gestational age used in Brazil [19].

All data were entered into MS-Excel spreadsheets and analyzed using the statistical software package Stata version 12.0 (Stata Corp., Texas, USA, 2015). Demographic, clinical, and laboratory variables, along with comorbidities, incident complications, and deaths, were

described. Survival and Cox regression analysis were performed to identify the most significant risk factors associated with mortality. The survivors were censored on the day of the patients' discharge from the ICU. Hazard ratios (HR) and its 95% confidence interval (CI95%) were used to quantify the associations. Any covariate with a p-value < 0.2 was considered a potential confounding factor and included in a multivariate Cox regression model. The inclusion of covariates in the model was carried out using the backward stepwise method.Due to collinearity with SOFA score, the serum creatinine level was not included in the final Cox regression model.After adjustment, a p-value of < 0.05 for two-sided tests was considered statistically significant, indicating that the covariate was deemed an independent risk factor for mortality.

RESULTS

We analyzed data from 149 patients admitted to the ICU of the study hospital. Table 1 displays their demographic, clinical, and laboratory profiles. Among these patients, 97 (65.1%) were female, with over two-thirds (n = 67) being pregnant or in the immediate postpartum period. Most were young adults under 50 years old (67.8%). The average duration of COVID-19 symptoms was 11 days (SD: 7.1), with only 11.0% reporting symptoms onset more than 15 days before ICU admission. Upon admission, 84.5% had aarterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2)≤ 300 and34.2% arrived under mechanical ventilation. Additionally, 63.1% had pre-existing comorbidities, with obesity (46.2%), arterial hypertension (26.9%), diabetes mellitus (16.8%), and chronic respiratory disease (12.8%) being the most common. Laboratory findings at admission revealed hypoalbuminemia and elevated levels of white blood cells, serum C-reactive protein, AST, and ALT. During their ICU stay, patients experienced a range of complications, including orotracheal intubation and mechanical ventilation (72.5%), acute kidney injury (32.9%), renal replacement therapy (21.5%), thromboembolic events (14.1%), and acute heart failure (6.7%). The median duration of ICU stay was 17 days (interquartile range: 8-30 days) for non-survivors and 16 days (interquartile range: 8-30 days) for survivors.All patients received corticosteroids, antibiotics, and prophylaxis for thromboembolism.

At the end of this cohort study, there were 38 deaths among 3,183 patient-days, resulting in an overall fatality rate of 1.2 deaths per 100 patient-days. The fatal cases occurred in18 (34.6%)male patients, in 29 (30.8%) with previous comorbidities and in 20 (39.2%) in mechanical ventilation at admission. The mean (SD) time of COVID-19 symptom onset was similar between survivors and non-survivors (p = 0.344).In both crude and adjusted analyses, the mean age (SD) of non-survivor patients was significantly higher than that of survivors

(57.5 *vs*40.0 years; p < 0.001).The laboratory finding upon the patient's ICU admission that showed independent association with death was the AST-to-ALT ratio (p < 0.001). SOFA score ≥ 2showed a trend to be associated to death in crude analysis, but this was not confirmed after adjustment (Table 2).

Table 1 – Demographic, clinical and laboratorial characteristics of patients with severe COVID-19 at admission to the intensive care unit in the Central Region of Brazil, from April 2020 to August 2021

Characteristics			**n**	**%**
Age (years)	*16 - 29*		36	24.2
	30 - 49		65	43.6
	50 - 69		22	14.8
	70 - 89		26	17.4
	Mean (SD):		44.4	18.9
Gender	*Female*		97	65.1
	Male		52	34.9
Pregnant/postpartum status (n=97 women)	*Yes*		67	45.0
	No		30	20.1
Days of symptoms onset (n=145)	*1 - 5*		15	10.3
	6 - 10		71	49.0
	11 - 15		43	29.7
	> 15		16	11.0
	Mean (SD):		11.0	7.1
Peripheral oxygen saturation at admission (%) (n=146)	*<90*		40	27.4
	90 - <95		40	27.4
	95 - 100		66	45.2
PaO2/FiO2 at admission (n=142)	*≤ 300*		120	84.5
	> 300		22	15.5
Mechanical ventilation at admission	*Yes*		51	34.2
	No		98	65.8
Previous comorbidities	*Yes*		94	63.1
	No		55	36.9
Reported comorbidity	*Obesity*		61	46.2
	High bloodpressure		40	26.9
	Diabetes mellitus		25	16.8
	Chronic respiratory disease		19	12.8
	Coronary artery disease		4	2.7
	Chronic heart failure		10	6.7
	Cancer		3	2.0
	Aids		2	1.3
Body mass index (kg/m^2) (n=132)	*< 25*		30	22.7
	25 - <30		41	31.1
	> 30		61	46.2
SOFA score at admission	*< 2*		17	11.4
	≥ 2		132	88.6
Complications during hospitalization	*Total requiring mechanical ventilation*		108	72.5
	Total with ARDS		120	80.5
	Acute kidney injury		49	32.9
	Need for renal replacement therapy		32	21.5
	Thromboembolic event		21	14.1
	Acute heart failure		10	6.7
	Bleeding event		8	5.4

	Acute arterial occlusion	5	3.4
	Acute liver failure	5	3.4
	Death	38	25.5
		Mean (SD)	
Laboratorial data at admission [Mean (SD)]	*White blood cells (/mm³)*	13738 (6633)	
	AST (U/L)	229 (1771)	
	ALT (U/L)	131 (756)	
	AST-to-ALT ratio	1.47 (1.03)	
	Albumin (g/dL)	2.8 (0.5)	
	Creatinine (mg/dL)	1.1 (1.2)	
	C reactive protein (mg/dL)	104 (125)	
	D-Dímer (ng/dL)	4.6 (8.7)	
		Median (IQ range)	
Duration of in-ICU stay (days)	*Non-survival*	17.0 (8.0 - 30)	
	Survivors	16.0 (8.0 - 30)	
	Total	16.0 (8.0 - 30)	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ICU: intensive care unit; SD: standard deviation; IQ: interquartile;ARDS: Acute respiratory distress syndrome;SOFA: sequential organ failure assessment.
Obs: Variation in the number of patients due to a lack of information.Total death: 38 in 3,183 patient-days at risk. Overall fatality: 1.2 death/100 patient-days.

Table 2 - Bivariate and multivariate analysis of the association between risk factors at admission and mortality of patients with severe COVID-19 in an intensive care unit in Central Brazil, April 2020 to August 2021

Potential risk fators		**Non-survivors** n (%)	**Survivors** n (%)	**Crude analysis**		**Adjusted analysis***	
				HR (CI95%)	**p**	**HR** (CI95%)	**p**
Gender	*Female*	20 (20.6)	77 (79,4)	1.00 (0.52;1.92)	0.999	-	-
	Male	18 (34.6)	34 (65,4)				
Previous comorbidities**	*Yes*	29 (30.8)	65 (69.2)	1.69 (0.80; 3.57)	0.171	-	0.620
	No	9 (16.4)	46 (83.6)				
Mechanical ventilation at admission	*Yes*	20 (39.2)	31 (60.8)	1.39 (0.73; 2.66)	0.318	-	-
	No	18 (18.4)	80 (81.6)				
SOFA score at admission	*< 2*	2 (11.8)	15 (88.2)	-	-	-	-
	≥ 2	36 (27.3)	96 (72.7)	0.36 (0.08; 1.67)	0.193	0.28 (0.06; 1.30)	0.105
Pregnant/ pospartum status	*Yes*	7 (10.4)	60 (89.6)	0.28 (0.11; 0.72)	0.008	-	0.817
	No	13 (43.3)	17 (56.7)				
		Mean(SD)					
Age (years)		57.5 (20.8)	40.0 (15.9)	1.04 (1.02; 1.05)	<0.001	1.04 (1.02; 1.07)	<0.001
Days of symptoms onset		11.6 (8.6)	10.8 (6.5)	1.02 (0.97; 1.08)	0.344	-	-
WBC count (/mm³)		16,113 (8,912)	12,925 (5,464)	1.00 (0.99; 1.00)	0.060	1.00 (1.00; 1.00)	0.017
Albumin (g/dL)		2.7 (0.4)	2.8 (0.5)	0.71 (0.36; 1.37)	0.305	-	-
C-reactive protein (mg/dL)		130.1 (124.0)	95.2 (124.1)	1.00 (0.99; 1.00)	0.968	-	-
D-dimer (ng/mL)		4.8 (4.3)	4.5 (9.8)	0.99 (0.94; 1.03)	0.594	-	-
AST-to-ALT ratio		1.9 (1.6)	1.3 (0.7)	1.26 (1.26; 1.91)	<0.001	1.80 (1.45; 2.24)	<0.001

*: Cox regression. Model parameters: LR chi^2: 39.8; p < 0,001. Pregnancy, comorbidities, and albumin at admission removed from the final model for non-significance by stepwise method.
** Patients with any of the following conditions (high blood pressure, chronic lung disease, diabetes mellitus, heart failure, coronary artery disease, cancer, aids or obesity).

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ICU: intensive care unit; SD: standard deviation; IQ: interquartile; HR: hazard ratio; WBC: white blood cell count; SOFA: sequential organ failure assessment.
Obs: Total death: 38 in 3,183 patient-days at risk. Overall fatality: 1.2 death/100 patient-days.Variation in the number of patients due to a lack of information for all patients.

Among female patients, there were a total of 20 deaths, accounting for 20.6% of the cases. Out of these, seven (10.4%) were among pregnant/postpartum women, which was lower than the number of deaths among non-pregnant women (p=0.008). However, after multivariate analysis, these proportions were found to be statistically similar between survivors and non-survivors (p=0.908).Due to the large number of pregnant and postpartum women, a subgroup analysis was conducted, excluding male participants. The results were consistent with the model using the full sample. Among female patients, death remained associated with increasing age (p = 0.043) and with AST-to-ALT ratio (p < 0.001), but not with pregnant/postpartum status or with white blood cells count(Table 3).

Table 3 - Multivariate analysis of the association between risk factors at admission and mortality among women(n = 97) with severe COVID-19 in an intensive care unit in Central Brazil, April 2020 to August 2021

Potential risk fators		**Non-survivors** n (%)	**Survivors** n (%)	**Crude analysis** **HR** (CI95%)	**p**	**Adjusted analysis*** **HR** (CI95%)	**p**
Pregnant/pospartum status	*Yes*	7 (10.4)	60 (89.6)	0.28 (0.11; 0.72)	0.008	-	0.860
	No	13 (43.3)	17 (56.7)				
Previous comorbidities**	*Yes*	14 (27.5)	37 (72.5)	1.93 (0.74; 5.05)	0.180	-	0.456
	No	6 (13.0)	40 (87.0)				
		Mean(SD)					
Age (years)		51.6 (21.6)	35.3 (14.6)	1.04 (1.01; 1.06)	0.001	1.04 (1.02; 1.07)	<0.001
WBC count (/mm^3)		16,512 (9,557)	12,707 (5,435)	1.00 (0.99; 1.01)	0.091	-	0.434
C-reactive protein (mg/dL)		144.5 (136.7)	67.3 (101.7)	1.01 (1.00; 1.01)	0.014	1.00 (0.99; 1.01)	0.057
SOFA score at admission	*< 2*	2 (14.3)	12 (85.7)	-	-	-	-
	≥ 2	18 (21.7)	65 (78.3)	0.27 (0.05; 1.42)	0.123	0.16 (0.03; 1.01)	0.051
AST-to-ALT ratio		1.5 (0.7)	2.3 (2.1)	1.49 (1.15; 1.95)	0.003	1.75 (1.33; 2.29)	<0.001

*: Cox regression. Model parameters: LR chi^2: 26.4; p < 0,001. Pregnancy, comorbidities, and albumin at admission removed from the final model for non-significance by stepwise method.
** Patients with any of the following conditions (high blood pressure, chronic lung disease, diabetes mellitus, heart failure, coronary artery disease, cancer, aids or obesity).
AST: aspartate aminotransferase; ALT: alanine aminotransferase; ICU: intensive care unit; SD: standard deviation; IQ: interquartile; HR: hazard ratio; WBC: white blood cell count; ;SOFA: sequential organ failure assessment.
Obs: Total death: 20 in 1,741 patient-days at risk. Overall fatality: 1.1 death/100 patient-days.Variation in the number of patients due to a lack of information for all patients.

DISCUSSION

In this case series of severely ill COVID-19 patients hospitalized in the ICU, we observed that respiratory failure and acute kidney injury were the primary causes of death in a medium-sized hospital in the Central Region of Brazil, which covers a vast, sparsely populated area in the middle of South America.The COVID-19 epidemic in this Region exhibited an explosive pattern, similar to the rest of the country. Simultaneous critical cases and limited healthcare system capacity led to the overload of emergency units and hospitals.

The severity of the analyzed cases is evident from the number of patients admitted to the unit who required mechanical ventilation or underwent this intervention during their ICU stay.The high frequency of death due to respiratory failure aligns with global and national reports [3,5,6,20].Similarly, AKI and thromboembolic events followed lung involvement as the most severe complications [21].

As expected, older age was associated with death, although comorbidities generally linked to old age were not. Although comorbidities, such asarterial hypertension, diabetes mellitus, and chronic pulmonary diseaseareassociated with death in several COVID-19 reports [1,6,20,22],they did not increase lethality in the present studyeven when analyzed clustered.Clinical frailty has been regarded as a superior predictor of a poorer prognosis in COVID-19 compared to age and comorbidities [23].Frailty scales were not applied to participants in this study, preventing us from assessing whether frailty was more influential than comorbidities in determining poor outcomes among the elderly in this sample.

In addition to age, a high AST/ALT ratio was the only laboratory predictor of in-ICU mortality in our study. Other biomarkers, such as creatinine, albumin, WBC count, and C-reactive protein, did not show an independent association with death in this sample. While AST and ALT are enzymes commonly used to identify liver injury, AST is also found in other organs like the heart, kidneys, skeletal muscles, red blood cells, and brain, making it less liver-specific than ALT. The elevated AST above ALT levels may suggest more severe liver involvement or systemic injury. This study's findings support the idea that an AST level higher than ALT may indicate a more severe form of COVID-19 [18,24].

SOFA score of 2 or more has a good prognostic accuracy for in-hospital mortality [25].In the present case series, initial SOFA of 2 or more was marginally associated with better survival. Although this lack of discriminatory capacity of SOFA score in this sample, it is important to emphasize that this criteria have limited usefulness in infectious respiratory failure as demonstrated during 2009 influenza A H1N1 pandemic [26].

Pregnancy has been considered a concerning factor for the development of severe COVID-19 [27]. In our case series, there was an overrepresentation of pregnant/postpartum

women due to the characteristics of the public health system in the study region. Despite both pregnant/postpartum and non-pregnant/postpartum women undergoing orotracheal intubation and mechanical ventilation at similar rates, the former group had better outcomes. When analyzing female patients separately, the predictors of poor outcomes were consistent across all patients, including increasing age and AST-to-ALT ratio, but not pregnancy/postpartum status. This suggests that gestational status may increase the risk of death among females but is less significant compared to old age. In sensitivity analysis, this finding underscores the strong association between COVID-19-related death and increasing age and AST-to-ALT ratio in our sample.

Interestingly, the lethality rate described here (25.5%) was lower than that demonstrated in the Brazilian average (36.9%). This comparison may not be appropriate because the present sample included a significant proportion of young women. However, mortality among pregnant/postpartum women in the present study (10.5%) was also lower than in pregnant women with COVID-19 throughout Brazil (26.1%) [28-30].Furthermore, patients who required MV also had a better prognosis in the present sample compared to the national average (35.2% vs. 65.0%) [31].It should be noted that many health services in Brazil were hastily establishedto face the pandemic.Lack of trained staff and material resources were a harsh reality in the country during the COVID-19 crisis.

This study has limitations that restrict the generalizability of the results. Firstly, the study sample was obtained from a single hospital. Additionally, there were limitations related to the small number of patients, which may have caused loss of study power and lack of statistical association as seen with SOFA score and comorbidities.Lack of serial collection of some tests, such as D-dimer, troponin, and procalcitonin, also limited the complete analyses in this study.

CONCLUSION

The clinical characteristics and risk factors for mortality of hospitalized patients with severe COVID-19 in ICU in Central Brazil was similar to those reported from the rest of the country and the world, with respiratory and renal failure being the most frequentevents leaving to poor prognosis. Increasing age and AST-to-ALT ratio were the best predictor of fatality. Almost half of the patients were pregnant or postpartum women, who had a better prognosis than the rest, likely due to the lower age and little comorbidities.

Ethical Approval

This study was approved by the Research Ethics Committee of Júlio Müller School Hospital under document number 4,820,226 on April 1st, 2021.

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