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HEALTH SCIENCES

Factors associated with mortality of patients with COVID-19 on invasive mechanical ventilation: A retrospective cohort study in a university hospital in Northeastern Brazil

THIAGO HENRIQUE M. SOARES, NELSON HENRIQUE L. DE MORAES, KARINA P.N.D. SOARES, MARIZÉLIA M. CARVALHO, ALESSANDRO S.S. HOLANDA, LARYSSA FERNANDA S. RODRIGUES, MARIA EDUARDA P. SILVA & PAULO ROBERTO C. CARVALHO

Abstract: The aim of this study is to identify the factors associated with mortality in patients with COVID-19 undergoing invasive mechanical ventilation at a university hospital in Northeastern Brazil. This is a retrospective cohort from April to August 2020 through an analysis of medical records, considering the demographic profile, comorbidities, complications, supports, respiratory and laboratory parameters. A total of 65 patients required invasive mechanical ventilation, of which 64.6% died in the ICU. They were older, had more comorbidities, shorter length of stay in the intensive care unit, received more support such as palliative care and two vasopressors simultaneously, showed lower levels of pH, hemoglobin and calcium, and higher levels of bicarbonate, lactate, prothrombin time, international normalized ratio, troponin and ferritin at the start of invasive mechanical ventilation. Furthermore, the time course of pH, arterial oxygen partial pressure to fractional inspired oxygen ratio, arterial carbon dioxide partial pressure, lactate, hemoglobin, platelets, lymphocytes, neutrophil-to-lymphocyte ratio, coagulation parameters, calcium, urea, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, ferritin, static compliance, airway resistance, tidal volume, and noradrenaline doses showed association with mortality. There was a high mortality rate in invasively mechanically ventilated COVID-19 patients, with some associated factors identified at the start of invasive mechanical ventilation and others identified over time.

Key words: COVID-19, critical care outcomes, intensive care unit, mechanical ventilation, mortality.

INTRODUCTION

The first case of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was reported in Wuhan, China, in 2019, spreading rapidly around the world (Huang et al. 2020). The World Health Organization (WHO) declared the COVID-19 pandemic on March 11, 2020 (Cucinotta & Vanelli 2020). Since then, humanity has experienced an unprecedented global public health crisis.

In this context, many individuals with COVID-19 required hospitalization, of which those who became critical were admitted to intensive care units (ICU) (Abate et al. 2021). Studies have reported high rates of need for invasive mechanical ventilation (IMV), and the mortality rate of patients requiring IMV was up to 92% (Hua et al. 2020, Lim et al. 2021).

Therefore, since the beginning of the pandemic, emerging studies have demonstrated factors associated with mortality in patients receiving IMV, such as age, sex, body mass index (BMI) comorbidities, respiratory parameters, biomarkers, treatments, organ support and complications during hospitalization (Battaglini et al. 2022, Biswas et al. 2021, Dessie & Zewotir 2021, Huang et al. 2021)

In this regard, several cohort studies reported the reality of ICUs facing COVID-19 with relevant scientific contributions. However, some methodological discrepancies were notable, especially when the laboratory and physiological data were collected at a single point, in which some authors considered the moment of hospital/UCI admission (Auld et al. 2020, Cummings et al. 2020, Richardson et al. 2020, Ziehr et al. 2020), while others considered the start of IMV (Botta et al. 2021, Estenssoro et al. 2021, King et al. 2020, Zangrillo et al. 2020).

However, since patients receiving IMV require a prolonged stay in the ICU, some authors have provided elucidations regarding changes over time in clinical and laboratory parameters as predictors of mortality, showing the importance of analyzing longitudinal data to assess patient prognosis and providing an expanded view of mortality risk factors (Ende et al. 2021, Patel et al. 2021, Zanella et al. 2021, Zangrillo et al. 2020, Zhou et al. 2020).

Accordingly, the aim of the present study was to evaluate factors associated with mortality, such as demographic data, comorbidities, supports and complications, and respiratory and laboratory parameters at the start of IMV and the time course over ten days of critically ill patients with COVID-19 admitted to an ICU of a public university hospital in Northeastern Brazil during the first wave of the pandemic. The primary outcomes of this study were COVID-19 mortality and survival and associated factors.

MATERIALS AND METHODS

A single-center, retrospective cohort study was conducted following current recommendations from the Strengthening the Reporting of Observational Studies in Epidemiology - STROBE (Von Elm et al. 2007) and was approved by the research ethics committee of Hospital das Clínicas, Universidade Federal de Pernambuco (CAAE: 30684520.5.1001.8807), with informed consent being waived.

Data were collected from all consecutive adult patients (≥18 years), diagnosed with COVID-19, admitted from April 18, 2020 to August 25, 2020, to the ICU at Hospital das Clínicas, Universidade Federal de Pernambuco, a quaternary public university hospital, one of the hospitals in Pernambuco state that provided care for critically ill patients with COVID-19 during the beginning of the pandemic, providing 22 exclusive ICU beds for patients with COVID-19.

All data were taken from medical records and laboratory databases. The collected variables included demographic data, signs and symptoms before hospital admission, comorbidities, use of resources and supportive therapy and complications during the ICU stay, length of stay in ICU and using IMV, respiratory and laboratory parameters at start of IMV and daily during the first 10 days, and mortality in the ICU.

The data were analyzed descriptively using absolute frequencies and percentages for categorical variables and median and interquartile range for numerical variables. The Pearson's Chi-squared test for categorical variables and Mann-Whitney test for numerical variables were used in comparing the two outcomes. However, Fisher's exact test was applied in the case in which the condition for using the Chi-squared test was not verified. The time course of each variable was presented in daily medians and quartiles and respective linear trend. Survival analysis was presented by Kaplan-Meier curves and the log-rank test was used to confirm the significance between different groups. The tests were applied considering statistically significant when $p<0.05$. All analyzes used the IBM program (SPSS) for Windows version 25.0, and Microsoft Excel 365 was used to plot the graphs.

RESULTS

There were 125 ICU admissions between April 18 and August 25, 2020, with 92 confirmed cases of COVID-19, of which 65 patients required IMV and were included in the analysis of this cohort. Thirty-six (55.4%) patients were male, with a median age (IIQ) of 61 (50-74) years, and 37 (56.9%) patients were over 60 years old. Men and women over 60 years had a mortality range of 86.4% and 80.0%, respectively. Compared to patients discharged from ICU, patients who died in the ICU had a higher median age (IIQ) [68 (58-77) versus 51 (41-61) years; $p<0.001$], and among patients aged 60 or over, 31 (74%) died ($p<0.001$) (Table I).

The median (IQR) BMI was 27.1 (22.6-30.8) kg/m^2, with 36 (55.4%) overweight or obese patients and 14 (21.5%) underweight patients (all older adults with BMI < 23 kg/m^2, according to the Pan American Health Organization 2001). There was no association between BMI and mortality (Table I). In addition, Figure 1 shows the proportion of patients according to age group, BMI classes and outcomes.

Kaplan-Meier curves demonstrate the survival percentage at 28 days for overall patients and stratified by age group, sex and BMI classes, with a significant difference only between age groups ($p<0.001$) (Figure 2).

All patients had one or more comorbidities and the most common were hypertension (36 [55.4%]), cardiovascular disease (25 [38.5%]), and diabetes mellitus (20 [30.8%]). Patients who died

Table I. Baseline characteristics, by outcomes.

		Outcome		
Characteristics	**Overall n=65 (100%)**	**Discharged from ICU n=23 (35.4%)**	**Died in ICU n=42 (64.6%)**	***p*-value**
Age (years)	61 (49.5-74)	51 (41-61)	68 (58-77)	< 0.001(2)*
Age group (years)				
<60	28/65 (43.1)	17/23 (73.9)	11/42 (26.2)	< 0.001(1)*
≥60	37/65 (56.9)	6/23 (26.1)	31/42 (73.8)	
Sex				
Male	35/65 (53.8)	13/23 (56.5)	22/42 (52.4)	0.749(1)
Body mass index (Kg/m^2)	27.1 (22.6-30.8)	30.2 (23-35.6)	26.7 (21.9-28.8)	0.522(2)
Body mass index classes				
Underweight	14 (21.5)	2 (8.7)	12 (28.6)	0.062(1)
Eutrophic	15 (23.1)	7 (30.4)	8 (19.0)	0.297(1)
Overweight and obesity	36 (55.4)	14 (60.9)	22 (52.4)	0.510(1)

Results expressed as n (%) or median (interquartile range). *p*-values were calculated using (1) Pearson's Chi-squared test and (2) Mann-Whitney test. * Significant difference at the 5.0% level.

in the ICU had comorbidities more frequently, with cancer being associated with mortality (p=0.045) (Table II).

The median (IQR) length of stay on IMV was 12 (8-17.5) days. Sixteen (24.6%) patients underwent extubation after a median time (IQR) of 15 (11-21) days and 12 (18.5%) underwent tracheostomy. Among tracheostomized patients, 6 (50%) were weaned successfully from IMV and discharged from ICU. There was an association with mortality with the length of stay in the ICU (p<0.001), IMV duration (p=0.011) and time with endotracheal tube (p=0.005) (Table II).

Regarding supportive care, 39 (60.0%) patients received neuromuscular blockade, 25 (38.5%) renal replacement therapy and 17 (26.2%) were placed in the prone position. The use of two vasopressor or inotropic drugs simultaneously (p=0.002) and palliative care (p=0.021) were associated with mortality (Table III).

Acute kidney injury and bronchospasm were the most frequent complications throughout the ICU stay, occurring in 17 (26.2%) and 16 (24.6%) patients, respectively. Although complications occurred more frequently in patients who died in the ICU, there were no significant differences, with emphasis on cardio-respiratory arrests [8 (19.0%) versus 1 (4.3%); p=0.142] (Table III).

Regarding arterial blood gases, respiratory parameters, noradrenaline doses (Table IV) and laboratory data (Table V) at the start of IMV, patients who died in ICU had lower median (IQR) levels of: pH [7.27 (7.20-7.33) versus 7.34 (7.28 -7.42); p=0.010], hemoglobin [10.50 (8.08-12.80) versus 13.10 (11.30-13.80) g/dL; p=0.022] and calcium [7.85 (7.50-8.40) versus 8.35 (7.98-8.80) mg/dL; p=0.015], and higher levels of: bicarbonate

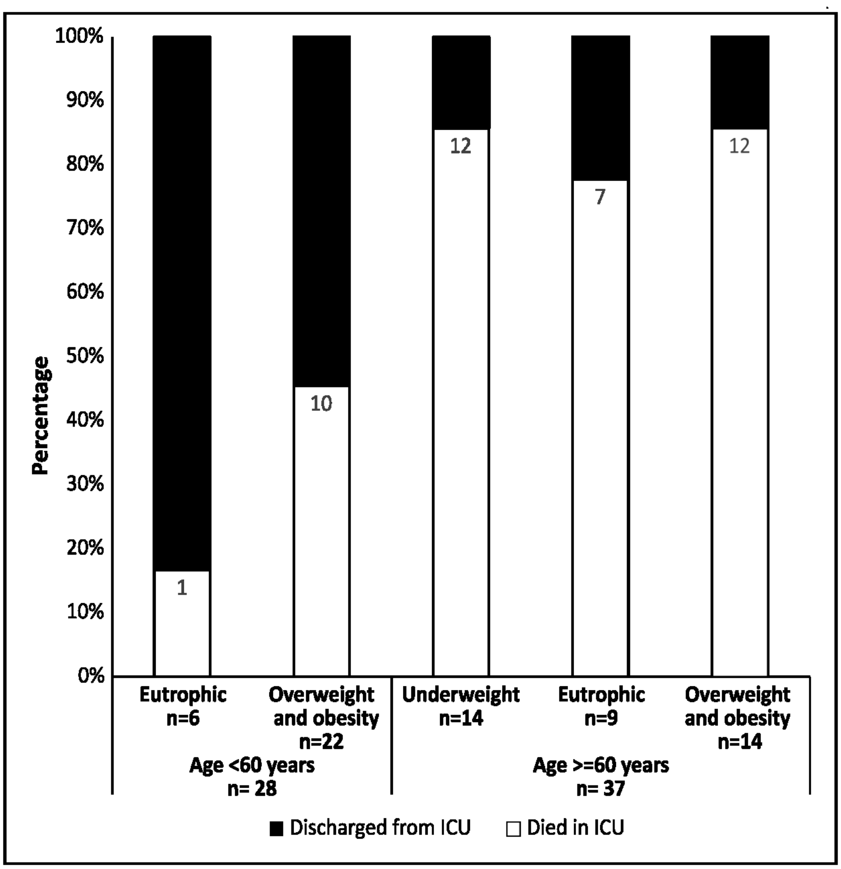

Figure 1. Proportion of patients according to age group, body mass index classes and outcomes. ICU: intensive care unit.

[25.40 (23-30) versus 22.65 (18.98-27.25) mmol/L; *p*=0.037], lactate [2.10 (1.10-3.40) versus 1.30 (0.75-2.00) mmol/L; *p*=0.047], prothrombin time [15.8 (14.65-16.95) versus 14.3 (13.93-15.98) s; *p*=0.012], international normalized ratio [1.24 (1.15-1.38) versus 1.11 (1.06-1.25); *p*=0.004], troponin [9.34 (4.85-145.1) versus 1.87 (0.75-11.14) ng/mL; *p*=0.013] and ferritin [2468 (1734-3563) versus 1770 (1078-2000) ng/mL; *p*=0.043].

Additionally, the time course of some variables also showed association with mortality. Figures 3 and 4 show the trends over the first 10 days on IMV in arterial blood gases levels, ventilation parameters, laboratory data and maximum noradrenaline levels in 24 hours.

Arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO_2/FiO_2), pH, bicarbonate, tidal volume, leukocytes, lymphocytes, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and ferritin showed a gradual increase in both groups. The PaO_2/FiO_2 ratio, pH, bicarbonate, platelets and lymphocytes were predominantly lower, and leukocytes, Vt, AST and ferritin were predominantly higher in

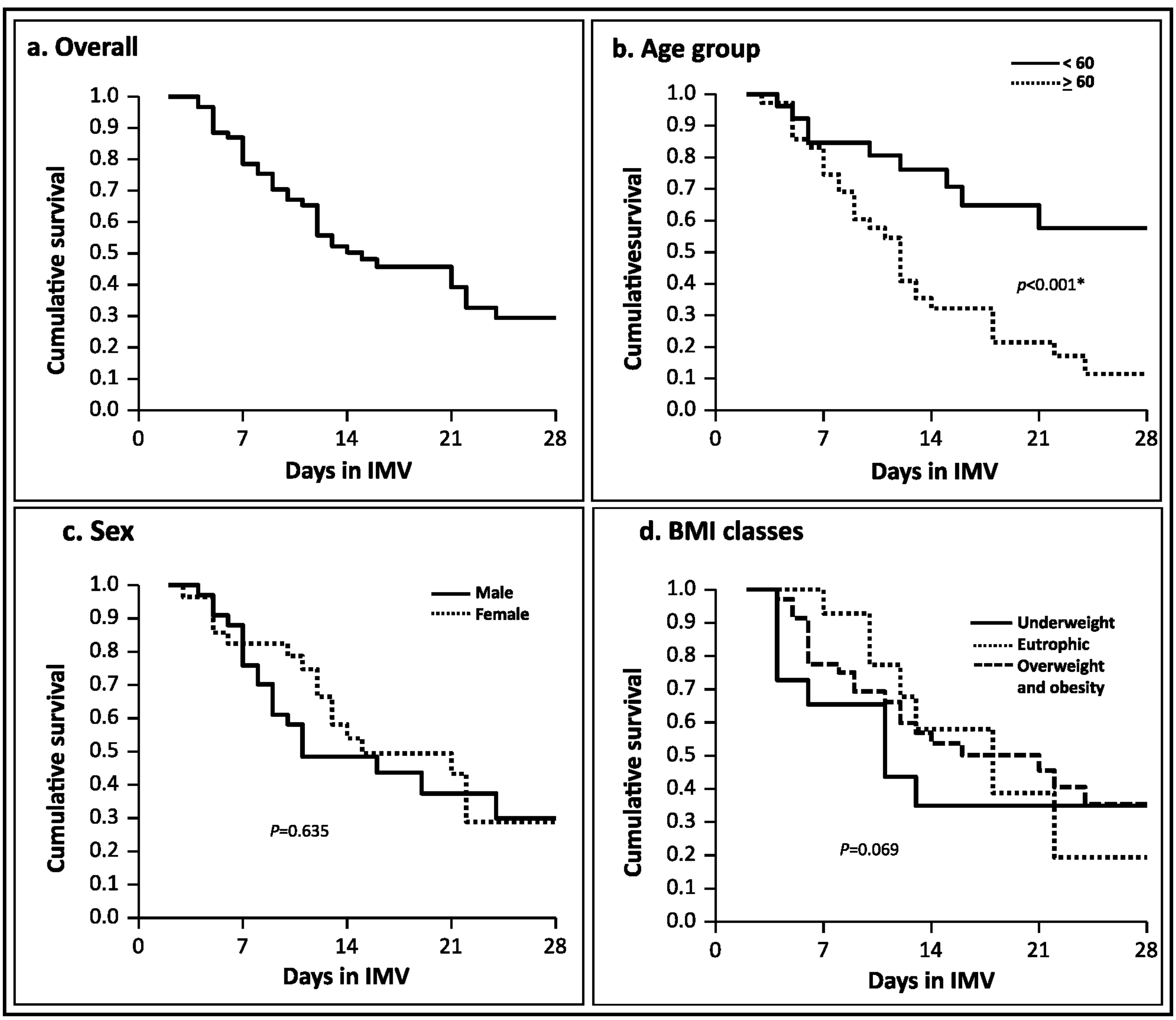

Figure 2. Kaplan-Meier survival curves for all patients and by age group, sex and body mass index classes. (a) Overall. (b) Age group. (c) Sex. (d) BMI classes. *p*-values were calculated using Log-rang test. *Significant difference at 5.0% level. BMI: body mass index; ICU: intensive care unit; IMV: invasive mechanical ventilation.

patients who died in the ICU. Bicarbonate, pH, lymphocytes, platelets and ferritin showed greater differences from the beginning of IMV until the tenth day. Compared to discharged patients, those who died in the ICU showed a more pronounced increase over 10 days in AST and ALT levels.

Other parameters showed different temporal trends, such as lactate, neutrophil-to-lymphocyte ratio (NLR), hemoglobin, D-dimer and C-reactive protein, with a gradual decrease in both groups. Hemoglobin concentrations were lower in patients who died in the ICU, while lactate and NLR were higher. There was a greater difference in hemoglobin, NLR and lactate concentrations.

Finally, other parameters showed antagonistic trends, such as arterial partial pressure of carbon dioxide ($PaCO_2$), driving pressure, static compliance, airway resistance, alkaline phosphatase, and levels of maximum noradrenaline dose in 24 hours, all showing worsening in patients who died in the ICU and improving in discharged patients. The differences between groups were most pronounced in $PaCO_2$, static compliance, airway resistance and noradrelaline doses.

DISCUSSION

In this single-center retrospective cohort study, we observed the experience from an ICU of a public federal university hospital during the beginning of COVID-19 pandemic, in which 7 out of every 10 patients required the use of IMV. From these, 2 out of 3 patients died. Patients

Table II. Comorbidities and time parameters, according to outcome. Results expressed as n (%) or median (interquartile range). *p*-values were calculated using (1) Pearson's Chi-squared test, (2) Fisher's Exact Test and (3) Mann-Whitney test. * Significant difference at the 5.0% level. COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; IMV: invasive mechanical ventilation; LOS: length of stay.

		Outcome		
Characteristics	**Overall n=65 (100%)**	**Discharged from ICU n=23 (35.4%)**	**Died in ICU n=42 (64.6%)**	***p*-value**
Comorbidities				
Hypertension	36 (55.4)	16 (69.6)	20 (47.6)	0.054(1)
Overweight and obesity	36 (55.4)	14 (56.5)	22 (21.4)	0.510(1)
Cardiovascular disease	25 (38.5)	12 (52.2)	13 (31.0)	0.093(1)
Diabetes mellitus	20 (30.8)	8 (34.8)	12 (28.6)	0.604(1)
Nephropathy	21 (32.3)	5 (21.7)	16 (38.1)	0.178(1)
COPD	11 (16.9)	6 (26.1)	5 (11.9)	0.176(2)
Cancer	7 (10.8)	-	7 (16.7)	0.045(2)*
Immune dysfunction	5 (7.7)	-	5 (11.9)	0.152(2)
Time parameters (days)				
ICU LOS	13 (7-21)	21 (14.-27)	9.5 (5-14.5)	<0.001(3)*
IMV LOS	12.00 (8-17.5)	15(11-21)	10 (6-14.25)	0.011(3)*
Endotracheal tube LOS	12.00 (7.5-16)	15(11-20)	10 (6-14)	0.005(3)*
Time to tracheostomy	20.50 (15.5-23.5)	20.5(16.25-24)	19 (15-22.5)	0.771(3)
Tracheostomy LOS	10.00 (7.5-24.25)	15(9-33)	8 (4-24)	0.134(3)

who died were: older; had more comorbidities; had a shorter length of stay in the ICU and using IMV; needed more supportive treatment; had more complications; showed worse levels in respiratory and laboratory parameters at the start of IMV and over time.

Other studies in Brazil have reported similar results regarding the morality rate, being around 51% in patients admitted to the ICU (Zimmermann et al. 2021), and even higher (59.5% to 80%) among those who required IMV (Ranzani et al. 2021, Marcolino et al. 2021). In contrast, a single-center study in a private hospital showed a less drastic mortality rate, 11.7% among those admitted to the ICU, and 34.1% among those who required IMV. The authors attributed this discrepancy to differences in the hospital network (private compared to public), criteria adopted for hospital and/or ICU admission, availability of resources and characteristics of ICU teams (Corrêa et al. 2021).

The association between advanced age, BMI and comorbidities with mortality has been widely reported by different authors (Biswas et al. 2021). A recent review also related the influence of comorbidities on the trajectory and severity of COVID-19, emphasizing heart disease, chronic kidney disease and cancer, being close

Table III. Supportive treatments and complications, according to outcome. Results expressed as n (%) or median (interquartile range). *p*-values were calculated using (1) Pearson's Chi-squared test and (2) Fisher's Exact Test. * Significant difference at the 5.0% level. ICU: intensive care unit.

		Outcome		
Characteristics	**Overall n=65 (100%)**	**Discharged form ICU n=23 (35.4%)**	**Died in ICU n=42 (64.6%)**	***p*-value**
Supportive treatments				
Neuromuscular blockade	39 (60.0)	15 (65.2)	24 (57.1)	0.525 (2)
Renal replacement therapy	25 (38.5)	9 (39.1)	16 (38.1)	0.935 (2)
One vasopressor	28 (43.1)	12 (52.2)	1 (38.1)	0.273 (2)
Two vasopressors	22 (33.8)	2 (8.7)	20 (47.6)	0.002 (2)*
Prone position	17 (26.2)	7 (30.4)	10 (23.8)	0.561 (2)
Palliative care	9 (13.8)	-	9 (21.4)	0.021*
Chest drain	6 (9.2)	2 (8.7)	4 (9.5)	1.000 (1)
Complications				
Acute kidney injury	17 (26.2)	7 (30.4)	10 (23.8)	0.561 (2)
Bronchospasm	16 (24.6)	4 (17.4)	12 (28.6)	0.317 (2)
Cardiac arrest	9 (13.8)	1 (4.3)	8 (19.0)	0.142 (1)
Unplanned extubation	6 (9.2)	3 (13.0)	3 (7.1)	0.657 (1)
Sepsis	4 (6.2)	-	4 (9.5)	0.288 (1)
Pleural effusion	4 (6.2)	-	4 (9.5)	0.288 (1)
Pneumothorax	3 (4.6)	1 (4.3)	2 (4.8)	1.000 (1)
Deep vein thrombosis	3 (4.6)	1 (4.3)	2 (4.8)	1.000 (1)
Stroke	3 (4.6)	-	3 (7.1)	0.547 (1)

to that observed in this cohort (Russell et al. 2023). Our results regarding BMI were also similar with the literature, which suggests that low weight and obesity as important predictors of mortality (Huang et al. 2021).

On average, the time from the onset of symptoms to full recovery is quite variable and may depend on several factors. We can similarly compare this fact with hospitalized patients, especially those who require intensive care. A prospective cohort study observed a length of stay in the ICU and IMV of 13 and 11 days, respectively, which is similar to what was observed in our results (Estenssoro et al. 2021).

In fact, many supportive treatments were needed throughout the days in ICU. Studies have shown the need for vasopressor or inotropic drugs in most critically ill patients with COVID-19 and related this need to increased mortality (Mermiri et al. 2023). A cohort study found that 76% of patients required one drug and 22% two drugs simultaneously and observed that the time course of the noradrenaline dose showed an increase among patients who died in ICU and a reduction in discharged patients, which is similar to our study (Thomson et al. 2020). Another retrospective cohort study showed that 36 (81.8%) of 44 patients on IMV who were in palliative care died (Sheehan et al. 2023).

Table IV. Arterial blood gas parameters, ventilator and respiratory parameters and maximum noradrenaline dose in 24 hours at the start of invasive mechanical ventilation, according to the outcome. Results expressed as n (%) or median (interquartile range). *p*-values were calculated using Mann-Whitney test. *Significant difference at 5.0% level. ICU: intensive care unit; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2/FiO_2: partial arterial oxygen pressure/inspired oxygen fraction; PBW: predicted body weight; PEEP: positive end-expiratory pressure.

		Outcome		
Characteristics	**Overall n=65 (100%)**	**Discharged from ICU n=23 (35.4%)**	**Died in ICU n=42 (64.6%)**	***p*-value**
Arterial blood gas parameters				
pH	7.30 (7.21-7.39)	7.34 (7.28-7.42)	7.27 (7.20-7.33)	0.010*
PaO_2 (mmHg)	89.4 (67.6-106.5)	91 (63-99.3)	85.50 (68-110.5)	0.602
$PaCO_2$ (mmHg)	45 (35.15-63.5)	45.8 (33-79)	44(35.45-63.25)	0.992
Bicarbonate (mmol/L)	24 (19.9-28.6)	25.4 (23-30)	22.65 (18.98-27.25)	0.037*
PaO_2/FiO_2 (mmHg)	167.9 (106.45-232)	140(97.4-232)	170 (126.75-232.65)	0.752
Lactate (mmol/L)	1.75 (0.93-2.68)	1.3 (0.75-2)	2.1 (1.1-3.4)	0.047*
Ventilator and respiratory parameters				
Static compliance (ml/cmH_2O)	36 (27-48)	34.6 (28-41)	36.50 (26.93-50)	0.372
Airway resistance (cmH_2O/L/s)	15 (11.50-17)	14 (10-16)	15 (11.75-17.25)	0.367
Driving pressure (cmH_2O)	11 (9-13)	12 (10-14)	11 (9-13)	0.160
PEEP (cmH_2O)	10 (8-12)	11.5 (9.5-12)	10 (8-11.5)	0.062
Plateau pressure (cmH_2O)	21 (17.75-23)	22 (20-24)	20(17-23)	0.218
Tidal volume (ml/kg PBW)	6.1 (5.4-6.65)	5.75 (5.3-6.33)	6.1 (5.4-6.8)	0.325
Maximum noradrenaline dose in 24 hours (mcg/kg/min)	0.14 (0.08-0.27)	0.18 (0.10-0.25)	0.14 (0.06-0.28)	0.533

Palliative care was also required for some patients in this study, none of whom survived.

A multicenter observational Italian study reported the use of non-invasive ventilation (NIV) and high flow nasal cannula before the intubation influencing liberation from IMV in 28 days. The authors demonstrated that the use of these resources did not have positive impacts

Table V. Laboratorial data levels at the start of invasive mechanical ventilation, according to outcome. Results expressed as n (%) or median (interquartile range). *p*-values were calculated using Mann-Whitney test. *Significant difference at 5.0% level. APTT: activated partial thromboplastin time; ICU: intensive care unit; INR: international normalized ratio; PT: prothrombin time.

		Outcome		
Characteristics	**Overall n=65 (100%)**	**Discharged from ICU n=23 (35.4%)**	**Died in ICU n=42 (64.6%)**	***p*-value**
Hemoglobin (g/dL)	11.90 (9.35-13.45)	13.1 (11.3-13.8)	10.95 (9.08-12.8)	0.015*
White blood cell (cells/µL)	12920 (8240-16375)	14230 (8940-18050)	10795 (7650-15305)	0.212
Platelet (10^3 cells/µL)	255 (147.5-336)	298 (203-339)	233.5 (97.5-312)	0.073
Neutrophils (cells/µL)	8390 (7870-8645)	8310 (7790-8770)	8395 (7978-8633)	0.631
Lymphocytes (cells/µL)	670 (480-1135)	730 (4800-1090)	640 (478-1148)	0.660
Neutrophil-to-lymphocyte ratio	12.16 (7.06-18.33)	11.38 (7.15-17.58)	12.97 (6.93-18.81)	0.583
PT (s)	15.1 (14.25-16.85)	14.3 (13.93-15.98)	15.8 (14.65-16.95)	0.012*
INR	1.19 (1.1-1.35)	1.11 (1.06-1.25)	1.24 (1.15-1.38)	0.004*
APTT (s)	36.3 (30-41)	34.7 (28.1-38.88)	37.60 (32.2-44.7)	0.053
Fibrinogen (mg/dL)	672 (525-789.5)	698.5 (562.5-803.75)	663 (506-780.50)	0.409
D-Dimer (ng/mL)	3495 (1777.5-9697.5)	3280 (1547.9-6650)	3920 (1974-10645)	0.236
Sodium (mmol/L)	140.1 (136.2-145.05)	142.5 (136-145)	139.1 (136.2-145.35)	0.489
Potassium (mmol/L)	4.5 (4.2-5.2)	4.4 (4.2-5)	4.75 (4.18-5.43)	0.190
Calcium (mg/dL)	8.1 (7.6-8.6)	8.35 (7.98-8.8)	7.85 (7.5-8.4)	0.015*
Magnesium (mg/dL)	2.5 (2.2-2.7)	2.5 (2.-2.75)	2.5 (2.2-2.7)	0.862
Blood urea nitrogen (mg/dL)	76.75 (44.13; 120.35)	64 (41-86.2)	87.8 (44.3-135)	0.110
Serum creatinine (mg/dL)	1.6 (0.85-3)	1.5 (0.9-2.2)	1.9 (0.8-3.4)	0.819
Aspartate aminotransferase (U/L)	47.50 (33-72.70)	48.45 (30.03-70.83)	47.4 (34.2-74.4)	0.478
Alanine aminotransferase (U/L)	37.8 (25.25-65.8)	42.85 (35.38-0.45)	34.1 (21-48.8)	0.094
Total bilirubin (mg/dL)	0.6 (0.4-0.9)	0.5 (0.4-0.78)	0.7 (0.48-1.1)	0.124
Alkaline phosphatase (U/L)	254.9 (186.05-371.30)	240.4 (196.70-362.60)	264.25 (172.73-388.45)	0.709
Troponin (ng/mL)	7.82 (1.63-28.7)	1.87 (0.75-11.14)	9.34 (4.85-145.1)	0.013*
Ferritin (ng/mL)	2300 (1184-2800)	1770 (1078-2000)	2468 (1734-3563)	0.043*
Creatine phosphokinase (U/L)	184.3 (94.43-564.93)	291.3 (96.2-631.8)	169.2 (83.5-559.9)	0.361
C-reactive protein (mg/dL)	20.4 (12.95-29.65)	18.74 (13.55-26.83)	21.7 (12.6-30.15)	0.743
Albumin (g/dL)	3.3 (2.9-3.6)	3.5 (3-3.7)	3.2 (2.7-3.6)	0.115

on the liberation of IMV (Gamberini et al. 2020). In our ICU, the use of NIV at the beginning of the pandemic was not recommended due to the risk of spreading contaminated aerosols, which would increase the risk contagion among the care team. Therefore, only one patient received NIV before intubation and was discharged from the ICU. The high-flow nasal cannula was not available.

In a previous study, the positive effects of the prone position (PP) for patients with COVID-19 who required IMV were reported, showing that a sustained oxygenation response after the first session of PP was a predictor of survival

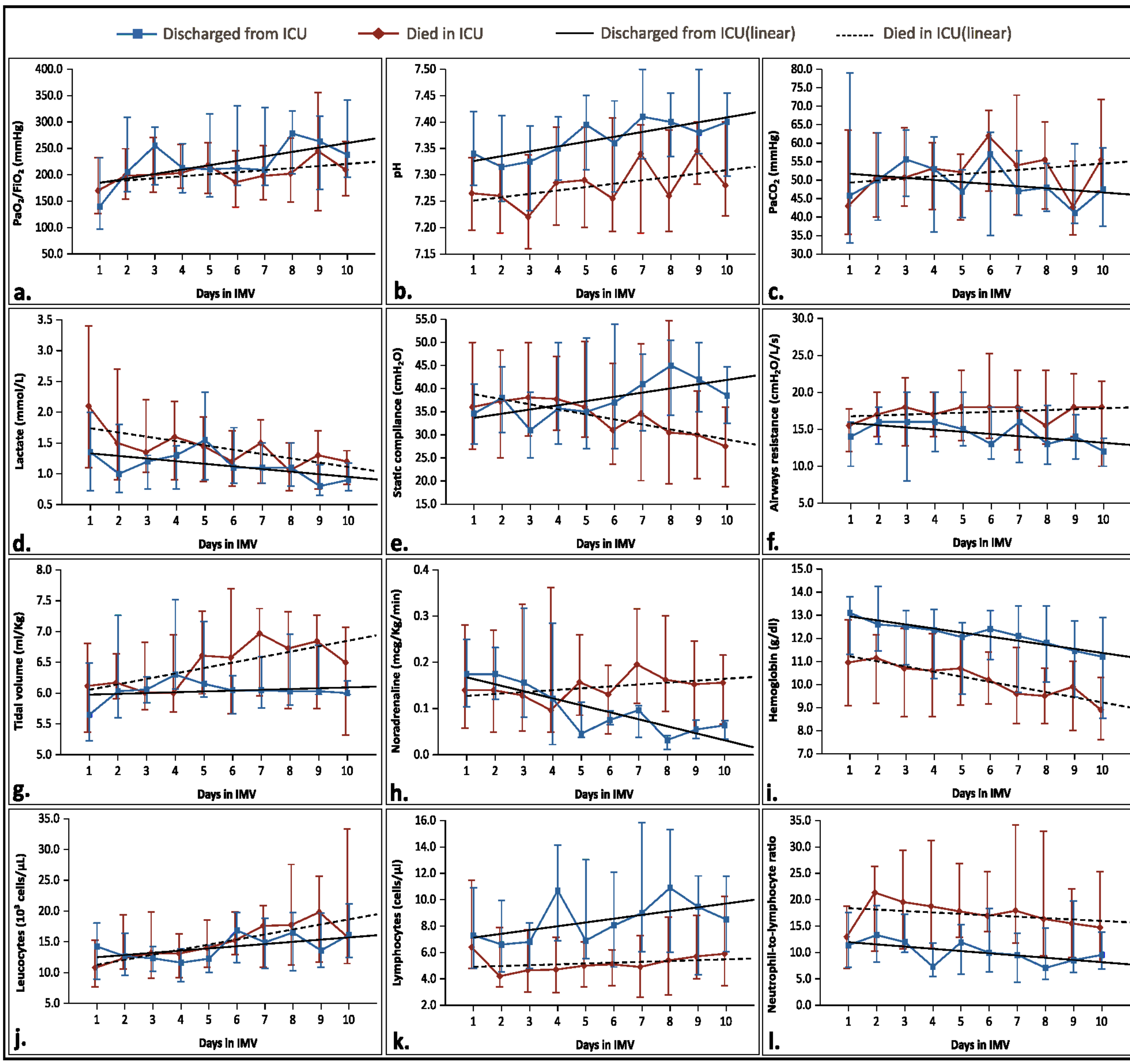

Figure 3. Time course of respiratory parameters, noradrenaline dose and laboratory parameters, according to the outcome. (a) PaO_2/FiO_2. (b) pH. (c) $PaCO_2$. (d) Lactate. (e) Static compliance. (f) Airways resistance. (g) Tidal volume. (h) Noradrenaline. (i) Hemoglobin. (j) Leucocytes. (k) Lymphocytes. (l) Neutrophil-to-lymphocyte ratio. The points are medians and the error bars represent the quartiles; solid lines and dotted lines represent linear trends over time. ICU: intensive care unit; IMV: invasive mechanical ventilation; PaO_2/FiO_2: Arterial partial pressure of oxygen to inspired oxygen fraction ratio; $PaCO_2$: Arterial partial pressure of carbon dioxide.

in the ICU and the oxygenation improvement to PP was not related to changes in respiratory mechanics (Scaramuzzo et al. 2021). The authors suggest that these early findings could be useful in informing who may benefit from a further level of assistance. In this cohort, we found no association of PP with mortality.

Thromboembolic complications and acute kidney injuries stand out among the complications most reported by different authors in patients with COVID-19 on IMV (Castro et al. 2021). Furthermore, there are also reports of cardiac arrests in critically ill patients with COVID-19 and presenting a high chance of having negative outcomes, as shown in a meta-analysis

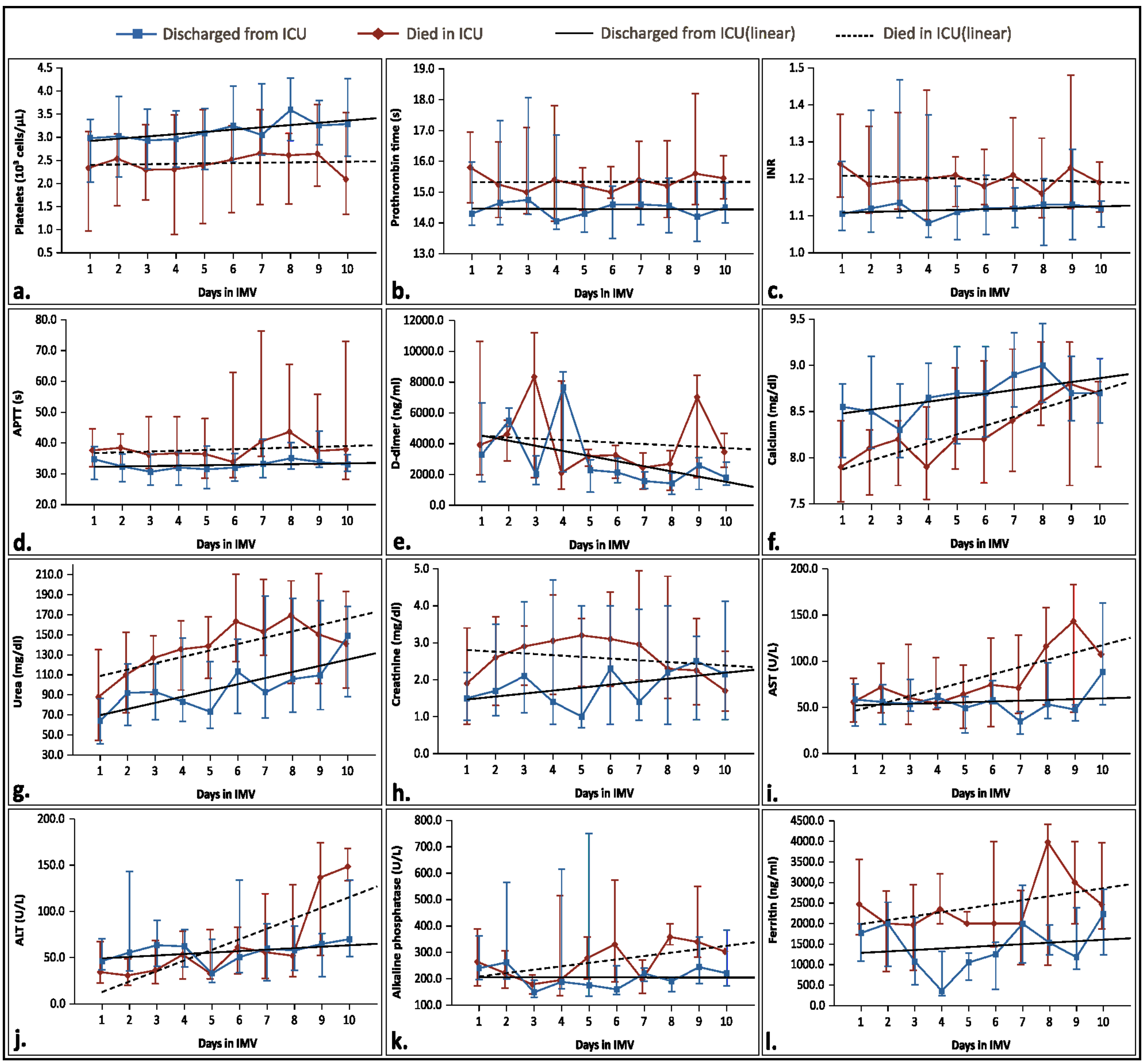

Figure 4. Time course of laboratory parameters, according to the outcome. (a) Platelets. (b) Prothrombin time. (c) INR. (d) APTT. (e) D-dimer. (f) Calcium. (g) Urea. (h) Creatinine. (i) AST. (j) ALT. (k) Alkaline phosphatase. (l) Ferritin. The points are medians and the error bars represent the quartiles; solid lines and dotted lines represent linear trends over time. ICU: intensive care unit; IMV: invasive mechanical ventilation; INR: international normalized ratio; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

with 10 studies with a total of 1.179 patients with COVID-19 who suffered cardiac arrest and of which approximately 90% died (Ippolito et al. 2021). We observed similar findings in our cohort.

In a review of 26 studies, relevant data was brought forward regarding several questions about respiratory mechanics, gas exchange and IMV settings in patients with COVID-19 admitted to ICUs. Data from the first 24 hours on IMV were identified: ventilation mode (volume-controlled ventilation), tidal volume (5.6 to 7.5 ml/kg of predicted body weight), PEEP (9 to 16.5 cmH_2O), plateau pressure (20.5 to 31 cmH_2O), driving pressure (9.5 to 15 cmH_2O), static compliance (24 to 49 ml/cmH_2O) (Grasselli et al. 2021). Our data regarding IMV parameters also showed values close to these ranges of variations, but there was no data that indicated an association with mortality.

Since the beginning of the pandemic, researchers have focused on identifying laboratory markers as predictors of mortality, including those that yield similar results in this cohort regarding: low pH (Ende et al. 2021), anemia (Wang et al. 2022), hypocalcemia (Martha et al. 2021), elevated blood lactate (Carpenè et al. 2022), elevated prothrombin time (Long et al. 2020), elevated international normalized ratio (Zinellu et al. 2021), elevated troponin (Lombardi et al. 2020) and elevated ferritin (Kaushal et al. 2022). It is worth noting that most studies published in this context showed data from admission day, or from isolated days of collection, without the concern of considering the start of IMV as a milestone of severity, nor of observing trends over time and their association with the mortality.

Studies have shown many variables associated with mortality regarding temporal trends (Ende et al. 2021, Patel et al. 2021, Zanella et al. 2021, Zangrillo et al. 2020, Zhou et al. 2020), a fact which has increasingly shown to be of great importance for managing and monitoring patients who, in most cases, remain hospitalized for a prolonged time and which was also demonstrated in this cohort.

The main strengths of this study are the demonstration of the reality experienced in an ICU of a public university hospital in Northeastern Brazil in the first wave of the pandemic; the methodological conception, which considers the starting day of IMV as initial milestone of critical status for data collection purposes; and the concern to investigate the time course of variables over time.

However, there were also some limitations; first, because it was a single-center study which represents the reality of a single public service, and so generalization to other locations is not recommended. Second, the small size of the sample studied, which made other types of analyzes that could provide clarification difficult. Although the Northeast region was one of the regions with the highest hospitalization and mortality rates among regions in Brazil, our ICU only had 22 beds for patients with COVID-19, which resulted in a small number of admissions at the beginning of the pandemic. Third, variables were only evaluated from the first to the tenth day of IMV, but there is some possibility that these temporal trends varied from this time onwards. Fourth, the study only covered critical patients from the first wave of the pandemic, a fact which would not represent a similar reality in the following phases.

Therefore, critical patients with COVID-19 admitted to the ICU of a public university hospital using IMV had a high mortality rate, with associated factors such as: advanced age, comorbidities such as cancer and treatments such as palliative care. Furthermore, some respiratory and laboratory parameters at the start of IMV were associated with mortality, as well as the temporal changes of some respiratory and laboratory data and noradrenaline doses showed an increase in mortality, confirming results showed in previous studies. Such findings reinforce the importance of assessment data at the start of IMV and also for the follow-up course of these parameters, which can be done through implementing clinical protocols, analyzing indicators or even the use of artificial intelligence tools capable of characterizing the degree of mortality risk of each patient as soon as possible for better decision-making and formulating care strategies in diagnostic and therapeutic approaches of critically ill patients with COVID-19 or even other diseases which have similar characteristics.

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THIAGO HENRIQUE M. SOARES[1]
https://orcid.org/0000-0003-0078-3036

NELSON HENRIQUE L. DE MORAES[2]
https://orcid.org/0009-0000-7811-6546

KARINA P.N.D. SOARES[3]
https://orcid.org/0000-0003-3077-1933

MARIZÉLIA M. CARVALHO[1]
https://orcid.org/0000-0003-0473-8371

ALESSANDRO S.S. HOLANDA[4]
https://orcid.org/0000-0003-2652-3830

LARYSSA FERNANDA S. RODRIGUES[5]
https://orcid.org/0009-0009-4814-308X

MARIA EDUARDA P. SILVA[5]
https://orcid.org/0009-0006-5192-0749

PAULO ROBERTO C. CARVALHO[5]
https://orcid.org/0000-0002-1534-3503

[1]Programa de Pós-Graduação em Cirurgia, Universidade Federal de Pernambuco, Avenida Professor Moraes Rego, s/n, Cidade Universitária, 50670-420 Recife, PE, Brazil

[2]Universidade Católica de Pernambuco, Escola de Saúde e Ciências da Vida, Rua do Príncipe, 526, Boa Vista, 50050-900 Recife, PE, Brazil

[3]Universidade Federal de Pernambuco, Unidade Multiprofissional dos Hospital das Clínicas, Avenida Professor Moraes Rego, s/n, Cidade Universitária, 50670-420 Recife, PE, Brazil

[4]Faculdade Pernambucana de Saúde, Departamento de Educação Física, Avenida Marechal Mascarenhas de Moraes, 4861, Imbiribeira, 51150-000 Recife, PE, Brazil

[5]Universidade Federal de Pernambuco, Departamento de Educação Física, Avenida Professor Moraes Rego, s/n, Cidade Universitária, 50730-120 Recife, PE, Brazil

Correspondence to: **Paulo Roberto Cavalcanti Carvalho, Thiago Henrique Murcabel Soares**
E-mail: paulo.robertocarvalho@ufpe.br, tmucarbel@hotmail.com

Author contributions

Conceptualization, THMS, NHLM and PRCC.; methodology, THMS, NHLM, KPNDS, and PRCC; formal analysis, THMS, KPNDS, MMC, ASSH, LFSR. and MEPS; resources, THMS, MMC, ASSH, LFSR and MEPS; writing, THMS, KPNDS and PRCC. All authors have read and agreed to the published version of the manuscript.