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ORIGINAL ARTICLE

Clinical parameters related to morbidity and mortality in patients with COVID-19 on hospital admission in a tertiary hospital

Parâmetros clínicos relacionados à morbimortalidade em pacientes com COVID-19 na admissão hospitalar em um hospital terciário

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Abstract

Objective: to identify the relationship between morbimortality, nutritional status and biochemical markers at hospital admission and stay in hospitalized COVID-19 patients.

Methods: retrospective stud whose data were collected from the medical records of patients admitted with a diagnosis of COVID-19, confirmed by the reverse transcription polymerase chain reaction testing, who were hospitalized between April and November 2020 at a tertiary hospital in the state of Pernambuco, in Northeast Brazil.

Results: 217 medical records were included, of which 71.9% were from older adults. 70% of patients had peripheral oxygen saturation below 95% at admission, and 47.5% were admitted to the intensive care unit. Being an older adult (OR = 1.9; 95%CI: 1.0; 3.5, p=0.035), having diabetes (OR = 2.2; 95%CI: 1.2; 3.8, p=0.007) and combined diabetes and hypertension (OR = 1.9; 95%CI: 1.1; 3.5, p=0.023) were associated with intensive care unit stay, as well as lymphopenia and renal function impairment in the first day of hospital stay. The prevalence of overweight and obesity was 21.2% and 20.7%. There was a difference in body mass index between adults and older adults (30.6±6.3 kg/m² vs. 27.5±4.8 kg/m², p<0.001). There was 43.8% mortality, which was associated with advanced age, lower peripheral oxygen saturation, body mass index, and albumin values, and increased of urea, creatinine, C-reactive protein, lactate dehydrogenase, troponin T, and dimer values.

Conclusion: older adults were at a higher risk of intensive care unit stay and mortality and had lower body mass index. Patients with lower peripheral oxygen saturation values at admission died. Renal dysfunction, coagulation disorders, and increased inflammatory markers led to a greater risk of intensive care unit stay and mortality.

Keywords: inflammation, intensive care units, nutritional status, renal insufficiency, SARS-CoV-2.

Resumo

Objetivo: identificar a relação entre morbimortalidade, estado nutricional e marcadores bioquímicos na admissão e permanência hospitalar em pacientes hospitalizados com COVID-19.

Métodos: estudo retrospectivo cujos dados foram coletados dos prontuários de pacientes admitidos com diagnóstico de COVID-19, confirmado pelo teste de reação em cadeia da polimerase com transcrição reversa, internados entre abril e novembro de 2020, em um hospital terciário do estado de Pernambuco, no Nordeste do Brasil.

Resultados: foram incluídos 217 prontuários, sendo 71,9% de pacientes idosos. Na admissão hospitalar, 70% dos pacientes apresentaram saturação periférica de oxigênio abaixo de 95% e 47,5% foram admitidos na unidade de terapia intensiva. Ser idoso (OR = 1,9; IC95%: 1,0; 3,5, p=0,035), ter diabetes (OR = 2,2; IC95%: 1,2; 3,8, p=0,007) e diabetes e hipertensão combinadas (OR = 1,9; IC95%: 1,1; 3,5, p=0,023)

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associaram-se à internação em unidade de terapia intensiva, assim como a linfopenia e o comprometimento da função renal no primeiro dia de internação. A prevalência de sobrepeso e obesidade foi de 21,2% e 20,7%. Houve diferença no índice de massa corporal entre adultos e idosos (30,6±6,3 kg/m2 vs. 27,5±4,8 kg/m2, p<0,001). Houve mortalidade de 43,8%, que foi associada à idade avançada e menores valores de saturação periférica de oxigênio, índice de massa corporal e de albumina, e aumento nos valores de ureia, creatinina, proteína C reativa, lactato desidrogenase, troponina T e D-dímero. **Conclusão:** idosos apresentaram maior risco de permanência em unidade de terapia intensiva e mortalidade, além de menor índice de massa corporal. Pacientes com valores de saturação periférica de oxigênio mais baixos na admissão tiveram maior taxa de mortalidade. Disfunção renal, distúrbios de coagulação e aumento de marcadores inflamatórios levaram a um maior risco de internação em unidade de terapia intensiva e mortalidade.

Palavras-chave: estado nutricional, inflamação, insuficiência renal, unidade de terapia intensiva, SARS-CoV-2.

Introduction

In December 2019, a pneumonia outbreak was identified in Wuhan (China), which quickly spread to other countries, including Brazil. It was caused by the new coronavirus and led to severe acute respiratory syndrome (SARS). Later, the World Health Organization (WHO) officially named it COVID-19 (1). Coronaviruses are RNA viruses that cause respiratory infections in various animals, including birds and mammals. Currently, six types of coronaviruses that infect humans have been identified, which affect the respiratory system, gastrointestinal tract, kidneys, vascular endothelium, and heart, possibly causing multiple organ failures and death (2).

In the physiopathology of the SARS coronavirus-2 infection (SARS-CoV-2), protein spikes on the virus surface attach to the angiotensin-converting enzyme 2 (ACE2) receptor in these human organs, activating spike protein with transmembrane protease serine 2 (TMPRSS2). When attached to ACE2, SARS-CoV2 downregulates this enzyme and increases the levels of angiotensin II, which may lead to the deleterious effects of activating the renin-angiotensin-aldosterone system, such as vasoconstriction, changes in vascular permeability, myocardium remodeling, and acute pulmonary injury (3).

The nutritional status can influence the clinical outcome of infected patients, who are at potential risk of malnutrition (4). Patients with higher percentages in nutritional risk screening tend to have longer hospital stays and a greater risk of mortality (5). Obesity is also associated with the risk and severity of the disease. Obese patients are more likely to develop severe respiratory insufficiency and need artificial ventilation, with an odds ratio of 7.36 in relation to non-obese people (6). This nutritional condition is associated with decreased expiratory reserve volume, functional capacity, and complacency of the respiratory system. The increase in inflammatory cytokines in obesity may help increase morbidity in COVID-19 infections (7). Considering the comorbidities with the worst prognoses and the indicators and symptoms associated with malnutrition, nutritional risk in COVID-19 patients is defined by the presence of at least one of the following criteria: being 65 years or older, having a body mass index (BMI) below 20 kg/m^2, inappetence, persistent diarrhea, pulmonary diseases, asthma, immunosuppression, history of weight loss, renal insufficiency, insulin-dependent diabetes, and cardiopathies, including important arterial hypertension (8).

Lymphopenia is both a marker of malnutrition and a factor of negative prognosis in COVID-19 patients (9), increasing the risk of mortality (10).

Even though albumin is not a good nutritional marker in situations of stress, patients with more severe COVID-19 conditions have significantly lower levels of albumin, total proteins, and prealbumin than others at hospital admission (2). High levels of ferritin, which is considered a nutritional indicator of iron metabolism and a biomarker of inflammation, have been associated with mortality (11). Hence, the objective of this study was to identify the relationship between nutritional status and clinical markers associated with morbimortality in hospitalized COVID-19 patients.

Methods

This is a retrospective and observational study carried out from August 2020 to March 2021. Data were collected from the medical records of patients admitted with a diagnosis of COVID-19, confirmed by the RT-PCR testing (reverse transcription polymerase chain reaction), who were hospitalized between April and November 2020 at a tertiary hospital in the state of Pernambuco, in Northeast Brazil.

Exclusion criteria were medical records of pregnant and lactating patients, children, adolescents, individuals with suspected COVID-19 not confirmed by RT-PCR, patients hospitalized for treatment of other causes and medical records of patients who were still undergoing hospital treatment during the data collection period. The medical records of individuals who were transferred to other institutions during hospitalization for continuity of treatment were also excluded.

Clinical data present in the hospital triage form were collected, considering vital signs: such as peripheral oxygen saturation (SpO_2), heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) and comorbidities, in addition to age and sex. The presence of severe acute respiratory syndrome was defined when the SpO_2 was less than 95% on room air, as recorded on the institution's screening form. Intensive care unit (ICU) stay, biochemical parameters in the first 24 hours and on the seventh day of hospital stay, clinical outcome, weight, height, and BMI were also collected. Biochemical alterations were defined according to the reference values present in the laboratory reports. The classification of nutritional status by BMI followed the WHO (12) cutoff points for adults and Lipschitz (13) for the older people. BMI equal to or greater than 30 kg/m² was classified as obese.

Data were analyzed descriptively using absolute frequencies and percentages of categorical variables. As for numeric variables, the following measures were used: mean and standard deviation for variables with normal distribution, and median with interquartile range (IQR) between quartiles 1 and 3 for variables with absence of normality. The association between two categorical variables was assessed using Pearson's chi-square test, or Fisher's exact test when the condition was not verified using the chi-square test. Student's t test with equal variances or the Mann-Whitney test compared two categories in terms of numerical variables. Student's t test was chosen when the data had normal distribution, while the Mann-Whitney test was used in the absence of normality. The Shapiro-Wilk test verified normality and the Levene F test verified equality of variances. The significance level used in statistical test decisions was set at 5%. Data were tabulated in an Excel spreadsheet, and the IBM SPSS software version 25 was used for statistical calculations. The study was approved by the Ethics Committee for Research with Human Beings of the Academic Center of Vitória, Federal University of Pernambuco under number 4.137.328.

Results

The sample comprised 217 individuals, with a prevalence of 156 (71.9%) older adults, with a mean age of 68.0±14.5 years. Women were 119 (54.8%) of the study population. 103 (47.5%) patients needed ICU stay during hospitalization. 138 (63.6%) had arterial hypertension and 79 (36.4%) had diabetes mellitus; 70 individuals (32.3%) had both pathologies. Other comorbidities were reported, namely: 14 (6.4%) cardiovascular diseases – including coronary diseases, strokes, and cardiac insufficiency –, 6 (2.8%) asthma, 4 (1.8%) solid tumor neoplasia, 4 (1.8%) chronic obstructive pulmonary disease, 4 (1.8%) neurodegenerative diseases, 3 (1.4%) depression and mental disorders, 3 (1.4%) nephropathies, 2 (0.9%) dermatological conditions, and 1 (0.5%) respiratory allergies. 163 (75,1%) patients already had SARS at hospital admission.

The research identified 46 (21.2%) individuals with overweight and 45 (20.7%) obeses; 44 (20.3%) were eutrophic and 14 (6.5%) thin; 68 (31.3%) had no record of weight and height. The mean BMI was 30.6±6.3 kg/m² in adults and 27.5±4.8 kg/m² in older adults, with a significant difference between the two (p=0.001). 95 (43.8%) people died, and 43 (45.2%) deaths occurred in the first seven days of hospital stay. 122 (56.2%) patients were discharged from the hospital, with a median of 11 (IQR: 7; 19) days of hospital stay.

Considering cardiorespiratory parameters assessed at hospital admission, ICU stay was not related to HR, systolic arterial pressure (SAP) or diastolic arterial pressure (DAP) recorded at hospital admission. Cardiovascular parameters did not correlate with in-hospital mortalit, but lower SpO_2 values were related to ICU stay and death (**Table 1**). Patients who died were older than the ones who were discharged and had lower BMI values, in kg/m². A comparison analysis of BMI between adults who died and those who were discharged, and among older people who died and those who were discharged, showed no significant difference (data not shown).

TABLE 1 – Demographic, clinical, and nutritional parameters at hospital admission and their relationship with the need for ICU stay and outcomes in individuals hospitalized for COVID-19 at a tertiary hospital in Recife, Pernambuco, 2021.

Variable	ICU stay Yes	ICU stay No	N (Yes/No)	p-value	Outcome Death	Outcome Discharge	N (Death/ Discharge)	p-value
Age	69.1±12.5	66.8±14.8	103/114	0.233*	73.8±12.4	63.2±13.1	95/122	<0.00*
SpO^2	86.0 (75.0; 92.0)	92.0 (88.0; 94.0)	82/107	< 0.001ǂ	86.0 (75.0; 92.0)	92.0 (88.7; 94.0)	79/110	<0.00ǂ
HR	92.0 (82.0; 105.0)	98.5 (84.0; 107.7)	71/104	0.437ǂ	89.0 (81.0; 105.0)	99.0 (85.0; 108.0)	72/103	0.119ǂ
SAP	134.5 (119.5; 156.2)	136.0 (120.0; 156.0)	78/106	0.679ǂ	130.0 (118.5; 156.5)	140.0 (120.0; 156.0)	77/107	0.222ǂ
DAP	80.0 (68.5; 89.0)	80.0 (70.0; 90.0)	77/106	0.534ǂ	75.5 (65.2; 89.5)	80.0 (70.0; 90.0)	76/107	0.139ǂ
Weight	78.5 (67.0; 88.2)	75.00 (63.0; 90.0)	86/63	0.493ǂ	75.5 (65.0; 85.0)	79.0 (68.0; 90.0)	64/85	0.275ǂ
Height	1.7±0.1	1.6±0.1	86/63	0.128*	1.7±0.1	1.7±0.1	64/85	0.158ǂ
BMI	27.8 (24.9; 30.1)	28.2 (25.1; 31.9)	86/63	0.846ǂ	27.2 (24.5; 29.4)	29.3 (25.5; 32.7)	64/85	0.020(2)

BMI, body mass index; DAP, diastolic arterial pressure; HR, heart rate; ICU, intensive care unit; SAP, systolic arterial pressure; SpO2, peripheral oxygen saturation. *Student's t-test with equal variances; ǂ Mann-Whitney test.

Even though no difference in age was found between those who stayed in ICU and the general ward, being an older adult increased by almost two times the risk of ICU stays. Having diabetes with and without hypertension was also associated with a risk respectively 2.2 times and 1.9 times greater of needing intensive support (**Table 2**). No association between nutritional status and ICU stay was verified. Of the 155 patients with renal function tests within the first 24 hours of admission, 41 (26.4%) already had worsening renal function at the time.

TABLE 2 – Association of demographic, clinical, and nutritional variables with the need for ICU stay in individuals hospitalized for COVID-19 at a tertiary hospital in Recife, Pernambuco, 2021.

Variable	Yes n (%)	No n (%)	p-value	OR (95% CI)
Age group				
Adults	22 (36.1)	39 (63.9)		1.0
Older adults	81 (51.9)	75 (48.1)	0.035 †	1.9 (1.0 to 3.5)
Total Group	103 (47.5)	114 (52.5)		
Sex				
Females	55 (46.2)	64 (53.8)		1.0
Males	48 (49.0)	50 (51.0)	0.685†	1.1 (0.6 to 1.9)
Total Group	103 (47.5)	114 (52.5)		
Comorbidities				
Diabetes mellitus				
No	55 (40.4)	81 (59.6)		1.0
Yes	47 (59.5)	32 (40.5)	0.007†	2.2 (1.2 to 3.8)
Hypertension				
No	34 (44.2)	43 (55.8)		1.0
Yes	68 (49.3)	70 (50.7)	0.471†	1.2 (0.7 to 2.1)
Both diabetes and hypertension				
No	61 (42.1)	84 (57.9)		1.0
Yes	41 (58.6)	29 (41.4)	0.023†	1.9 (1.1 to 3.5)
Others				
No	78 (45.6)	93 (54.4)		1.0
Yes	24 (54.5)	20 (45.5)	0.290 †	1.4 (0.7 to 2.8)
Total Group	102 (47.4)	113 (52.6)		
SARS				
No	8 (33.3)	16 (66.7)		1.0
Yes	72 (44.2)	91 (55.8)	0.316†	1.6 (0.6 to 3.9)
Total Group	80 (42.8)	107 (57.2)		
Nutritional status				
Thinness	7 (50.0)	7 (50.0)		1.0
Normal	29 (65.9)	15 (34.1)	0.498†	1.9 (0.6 to 6.5)
Overweight	27 (58.7)	19 (41.3)		1.4 (0.4 to 4.7)
Obesity	23 (51.1)	22 (48.9)		1.0 (0.3 to 3.5)
Total Group	86 (57.7)	63 (42.3)		
Lymphopenia 24h				
No	15 (31.9)	32 (68.1)		1.0
Yes	80 (71.4)	32 (28.6)	0.001†	5.3 (2.5 to 11.1)
Total Group	95 (59.7)	64 (40.3)		
Lymphopenia 7 days				
No	21 (43.8)	27 (56.3)		1.0
Yes	31 (66.0)	16 (34.0)	0.030†	2.5 (1.1 to 5.7)
Total Group	52 (54.7)	43 (45.3)		
Thrombocytopenia 24h				
No	69 (58.5)	49 (41.5)		1.0
Yes	25 (71.4)	10 (28.6)	0.167†	1.8 (0.8 to 4.0)
Total Group	94 (61.4)	59 (38.6)		
Thrombocytopenia 7 days				
No	46 (57.5)	34 (42.5)		
Yes	8 (88.9)	1 (11.1)	0.083‡	*
Total Group	54 (60.7)	35 (39.3)		
Increased urea 24h				
No	50 (50.0)	50 (50.0)		1.0
Yes	44 (77.2)	13 (22.8)	0.001†	3.4 (1.6 to 7.0)
Total Group	94 (59.9)	63 (40.1)		
Increased urea 7 days				
No	25 (44.6)	31 (55.4)		1.0
Yes	30 (78.9)	8 (21.1)	0.001†	4.6 (1.8 to 11.9)
Total Group	55 (58.5)	39 (41.5)		
Increased creatinine 24h				
No	63 (55.3)	51 (44.7)		1.0
Yes	31 (75.6)	10 (24.4)	0.022†	2.5 (1.1 to 5.6)
Total Group	94 (60.6)	61 (39.4)		
Increased creatinine 7 days				
No	34 (51.5)	32 (48.5)		1.0
Yes	23 (79.3)	6 (20.7)	0.011†	3.6 (1.3 to 10.0)
Total Group	57 (60.0)	38 (40.0)		

CI, confidence interval; ICU, intensive care unit; OR, odds ratio; SARS, Severe acute respiratory syndrome.
* It could not be determined due to the very low frequency; †Pearson's chi-square test; ‡ Fisher exact test.

Increased urea and creatinine (both in the first 24 hours and on the seventh day of hospital stay) and lymphopenia were significantly associated with increased risk of ICU stay – more than 5 times greater in first 24-hour lymphopenia, 4.6 times greater in 7th-day increased urea, and 3.6 times greater in 7th-day increased creatinine. Patients who needed ICU stay had significantly lower lymphocyte and bicarbonate percentage values and higher urea, creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), creatine phosphokinase (CPK), D-dimer, ferritin, and C-reactive protein (CRP) in the first 24 hours after hospital admission, as shown in **Table 3**

TABLE 3 – Biochemical parameters in the first 24 hours of hospital admission and their relationship with the need for ICU stay in individuals hospitalized for COVID-19 at a tertiary hospital in Recife, Pernambuco, 2021.

Variable	Yes	No	N (Yes / No)	p-value
Hemoglobin (g/dL)	12.1±1.1	12.5±1.7	96/105	0.21*
Hematocrit (%)	36.4(32.5; 39.8)	37.3(34.6; 39.9)	96/105	0.20‡
Leukocytes (/µL)	7,650(5100; 11100)	6,800(5500; 9150)	96/105	0.13‡
Lymphocytes (/µL)	855.5(582; 1183.5)	940 (677; 1275)	96/105	0.21‡
% lymphocytes	11(8; 15.5)	14(10; 19.4)	96/104	0.004‡
Platelets (.10^3/µL)	201(142.5; 265.5)	214(176.5; 270.5)	96/105	0.14‡
ESR (mm)	35.5(21.5; 58.5)	43.0(25; 56.7)	22/20	0.61‡
Urea (g/dL)	45 (29; 74.5)	31(23; 52)	93/102	0.001‡
Creatinine (g/dL)	1.13(0.9; 1.9)	0.99(0.8; 1.2)	93/102	0.004‡
LDH (U/L)	406 (331.5; 589.5)	302 (233.5; 390)	65/69	<0.001‡
AP (U/L)	81 (69; 122)	79 (62; 101)	31/37	0.43‡
AST (U/L)	66.5 (41; 104)	47 (34; 66)	74/85	0.001‡
ALT (U/L)	49 (33.5; 84.5)	44 (28; 75)	73/85	0.21‡
GGT (U/L)	137.5 (81.7; 325.7)	96 (54; 199)	32/43	0.06
Bicarbonate (mmol/L)	25.98 ± 4.86	27.98 ± 3.88	45/48	0.030*
Troponin T (µg/L)	15.8 (7.2; 33.2)	12.1 (8; 26.6)	42/26	0.61‡
CPK (U/L)	168 (78; 261)	71.5 (43.5; 104.2)	35/30	0.001‡
Dimer (µg/mL)	1.64 (0.85; 4.07)	1.09 (0.63; 1.59)	54/48	0.007‡
Fibrinogen (mg/dL)	656 (547; 707)	658 (552.7; 736.7)	27/22	0.64‡
Albumin (g/dL)	2.84 ± 0.51	3.05 ± 0.32	24/21	0.10*
Ferritin (ng/dL)	1,649(941.9; 2567.0)	980.9.5; 1402.2)	23/26	0.021‡
CRP (mg/dL)	14.7 (10.0; 20.3)	11.4 (6.1; 16.3)	52/91	0.004‡

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; ICU, intensive care unit; LDH, lactate dehydrogenase. *Student's t-test with equal variances; ‡Mann-Whitney test.

Older adults had a much higher risk of mortality. Those who were hospitalized in the ICU, who had lymphocytopenia, thrombocytopenia and worsening of renal function within 24 hours of admission and on the 7th-day of hospitalization had an increased risk of mortality (**Table 4**).

TABLE 4 – Association of demographic, nutritional, and clinical variables with the clinical outcome of individuals hospitalized for COVID-19 at a tertiary hospital in Recife, Pernambuco, 2021.

Variable	Death n (%)	Discharge n (%)	p-value	OR (95% CI)
Age group	14 (23.0)	47 (77.0)		1.0
Adults	81 (51.9)	75 (48.1)	0.001ǂ	3.6 (1.8 to 7.1)
Older adults				
Sex				
Females	50 (42.0)	69 (58.0)		1.0
Males	45 (45.9)	53 (54.1)	0.564ǂ	1.2 (0.7 to 2.0)
ICU stay				
No	21 (18.4)	93 (81.6)		1.0
Yes	74 (71.8)	29 (28.2)	< 0.001ǂ	11.3 (6.0 to 21.4)
Total Group	95 (43.8)	122 (56.2)		
Comorbidities				
Diabetes mellitus				
No	55 (40.4)	81 (59.6)		1.0
Yes	39 (49.4)	40 (50.6)	0.203ǂ	1.4 (0.8 to 2.5)
Arterial hypertension				
Yes	60 (43.5)	78 (56.5)	0.923ǂ	1.0
No	34 (44.2)	43 (55.8)		1.0 (0.6 to 1.8)
Both diabetes and hypertension				
No	59 (40.7)	86 (59.3)		1.0
Yes	35 (50.0)	35 (50.0)	0.197ǂ	1.4 (0.8 to 2.6)
Others				
No	71 (41.5)	100 (58.5)		1.0
Yes	23 (52.3)	21 (47.7)	0.200ǂ	1.5 (0.8 to 3.0)
Total Group	94 (43.7)	121 (56.3)		
SARS				
No	6 (25.0)	18 (75.0)		1.0
Yes	72 (44.2)	91 (55.8)	0.075ǂ	2.4 (0.9 to 6.3)
Total Group	78 (41.7)	109 (58.3)		
Nutritional status				
Thinness	8 (57.1)	6 (42.9)	0.096ǂ	3.3 (0.9 to 11.3)
Normal	23 (52.3)	21 (47.7)		2.7 (1.1 to 6.5)
Overweight	20 (43.5)	26 (56.5)		1.9 (0.8 to 4.5)
Obesity	13 (28.9)	32 (71.1)		1.0
Total Group	64 (43.0)	85 (57.0)		
Lymphopenia 24h				
No	13 (27.7)	34 (72.3)		1.0
Yes	62 (55.4)	50 (44.6)	0.001ǂ	3.2 (1.5 to 6.8)
Total Group	75 (47.2)	84 (52.8)		
Lymphopenia 7 days				
No	10 (20.8)	38 (79.2)		1.0
Yes	20 (42.6)	27 (57.4)	0.023ǂ	2.8 (1.1 to 7.0)
Total Group	30 (31.6)	65 (68.4)		
Thrombocytopenia 24h				
No	50 (42.4)	68 (57.6)		1.0
Yes	23 (65.7)	12 (34.3)	0.015ǂ	2.6 (1.2 to 5.7)
Total Group	73 (47.7)	80 (52.3)		
Thrombocytopenia 7 days				
No	25 (31.3)	55 (68.8)		
Yes	8 (88.9)	1 (11.1)		*
Total Group	33 (37.1)	56 (62.9)		
Increased urea 24h				
No	34 (34.0)	66 (66.0)		1.0
Yes	41 (71.9)	16 (28.1)	0.001ǂ	4.9 (2.4 to 10.1)
Total Group				
Increased urea 7 days	75 (47.8)	82 (52.2)		
No	10 (17.9)	46 (82.1)		1.0
Yes	24 (63.2)	14 (36.8)	< 0.001ǂ	7.9 (3.1 to 20.4)
Total Group	34 (36.2)	60 (63.8)		
Increased creatinine 24h				
No	46 (40.4)	68 (59.6)		1.0
Yes	29 (70.7)	12 (29.3)	0.001ǂ	3.6 (1.6 to 7.7)
Total Group	75 (48.4)	80 (51.6)		
Increased creatinine 7 days				
No	17 (25.8)	49 (74.2)		1.0
Yes	19 (65.5)	10 (34.5)	< 0.001ǂ	5.5 (2.1 to 14.1)
Total Group	36 (37.9)	59 (62.1)		

CI, confidence interval; ICU, intensive care unit; OR, odds ratio; SARS, Severe acute respiratory syndrome.
* It could not be determined due to the very low frequency; ǂPearson's chi-square test; ǂ Fisher's exact test

Biochemical parameter assessment in the first 24 hours indicated that patients who died had a significantly lower relative number of lymphocytes and platelets, lower levels of bicarbonate and alanine aminotransferase (ALT), and higher serum levels of leukocytes, LDH, troponin T, CPK, D-dimer, urea, and creatinine than those who were discharged (**Table 5**). On the seventh day of hospital stay, besides these parameters, decreased albumin levels and increased CRP were also related to mortality. On the other hand, there was no difference in bicarbonate levels between the groups on the seventh day of the hospital stay (**Table 6**).

TABLE 5 – Biochemical parameters in the first 24 hours of hospital admission and their relationship with the clinical outcome in individuals hospitalized for COVID-19 at a tertiary hospital in Recife, Pernambuco, 2021.

Variable	Death	Discharge	N (Death / Discharge)	p-value
Hemoglobin (g/dL)	12.2 (11.0; 13.6)	12.5 (11.5; 13.4)	87 / 114	0.26*
Hematocrit (%)	35.9 (32.2; 39.8)	37.2 (34.8; 39.7)	87 / 114	0.16*
Leukocytes (/µL)	8,300 (5,100; 11,500)	6,800 (5,500; 9,025)	87 / 114	0.040*
Lymphocytes (/µL)	864 (612; 1,224)	886.5 (625.2; 1,228)	87 / 114	0.79*
%lymphocytes	11.0 (7.0; 16.4)	12.85 (9.4; 17.7)	87 / 112	0.07*
Platelets (.103/µL)	191(134; 244)	225.5 (180; 291)	87 / 114	0.001*
ESR (mm)	50.0 (25.8; 63.8)	35.0 (19.8; 50.0)	12 / 30	0.24*
Urea (g/dL)	55 (35; 97.5)	29 (22; 47)	84 / 111	<0.001*
Creatinine(g/dL)	1.3 (0.9; 1.9)	0.9 (0.7; 1.1)	84 / 111	<0.001*
LDH (U/L)	411 (317.5; 629.5)	316 (243.5; 394.5)	53 / 81	<0.001*
AP (U/L)	75 (55; 104)	82 (65; 117)	21 / 47	0.33*
AST (U/L)	60 (41; 97)	50 (36; 73.7)	67 / 92	0.05*
ALT (U/L)	40 (25; 63.25)	51.5 (35.2; 82.7)	66 / 92	0.046*
GGT (U/L)	120.5 (57.2; 204.5)	133.0 (62.5; 261.0)	22 / 53	0.54*
Bicarbonate (mmol/L)	27.0 (24.0; 28.5)	28.5(26.0; 30.8)	49 / 44	0.018*
Troponin T(µg/L)	0.0 (10.7; 12.7)	9.3 (6.0; 19.2)	32 / 36	0.001*
CPK (U/L)	142 (78; 253)	81.5 (47; 133.5)	27 / 38	0.020*
Dimer (µg/mL)	1.75 (1.08; 5.41)	1.02 (0.62; 1.62)	44 / 58	<0.001*
Fibrinogen (mg/dL)	609 (476; 692.5)	658 (563;734)	14 / 35	0.12*
Albumin (g/dL)	2.86±0.55	2.97±0.40	12 / 33	0.47ǂ
Ferritin (ng/dL)	1162.6 (739.6; 2318.7)	1102 (492.5; 1881.9)	16 / 33	0.54*
CRP (mg/dL)	13.7 (7.2; 20.1)	11.7 (7.0; 17.2)	44 / 99	0.12*

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; ICU, intensive care unit; LDH, lactate dehydrogenase. *Student's t-test with equal variances; ǂMann-Whitney test.

TABLE 6 – Biochemical parameters after 7 days of hospital admission and their relationship with clinical outcome of individuals hospitalized for COVID-19 at a tertiary hospital in Recife, Pernambuco, 2021.

Variable	Death	Discharge	N (Death / Discharge)	p-value
Hemoglobin (g/dL)	10.9±2.0	11.5±1.7	30 / 65	0.11*
Hematocrit (%)	32.4±5.8	34.0±4.8	30 / 65	0.18ǂ
Leukocytes (/µL)	12,250 (9,000; 17,675)	7,400 (5,800; 10,450)	30 / 65	0.001ǂ
Lymphocytes (/µL)	927 (650.5; 1,391.2)	1,180 (840; 1,621.5)	30 / 65	0.045ǂ
Lymphocytes (%)	6.5 (5; 11)	16.1(10; 24.7)	30 / 65	<0.001ǂ
Platelets (.103/µL)	228 (185; 326.75)	336.5 (277.75; 462.5)	30 / 64	<0.001ǂ
ESR (mm)	48.3±29.0	55.6±27.4	15 / 23	0.44*
Urea (g/dL)	112 (50.7; 193.5)	36 (23.5; 52.5)	30 / 61	<0.001ǂ
Creatinine (g/dL)	2.3 (0.9; 4.1)	0.95 (0.7; 1.2)	30 / 60	<0.001ǂ
LDH (U/L)	488 (448.5; 696)	304 (243.5; 365.7)	17 / 40	<0.001ǂ
AP (U/L)	109.5(77.7; 120.5)	82(54; 108)	14 / 19	0.08ǂ
AST (U/L)	50.5 (38.2; 88.7)	46 (36; 64.5)	20 / 45	0.317ǂ
ALT (U/L)	45 (33.2; 66.5)	69 (39.5; 95)	20 / 46	0.05ǂ
GGT (U/L)	229(107; 330.5)	199.5(78.5; 335.5)	13 / 20	0.52ǂ
Bicarbonate (mmol/L)	26 (22.5; 32.5)	28 (24.2; 29.7)	17 / 24	0.66ǂ
Troponin T(µg/L)	45(15.5; 182.5)	9.6(5.1; 19.3)	14 / 30	<0.001ǂ
CPK (U/L)	174 (107; 650)	60 (33; 78.5)	15 / 29	<0.001ǂ
Dimer (µg/mL)	7.66(3.49; 18.01)	1.81(0.79; 4.24)	21 / 40	< 0.001ǂ
Fibrinogen (mg/dL)	522.5(449; 760)	625 (587; 854)	14 / 19	0.07ǂ
Albumin (g/dL)	2.1±0.5	2.7± 0.5	17 / 25	<0.001*
Ferritin (ng/dL)	1415.5(578; 2974)	947.9(359; 1583.4)	15 / 31	0.07ǂ
CRP (mg/dL)	15.5(7.6; 27.7)	4.24(1.6; 8.8)	27 / 58	<0.001ǂ

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; ICU, intensive care unit; LDH, lactate dehydrogenase. *Student's t-test with equal variances; ǂMann-Whitney test. ǂMann-Whitney test

Discussion

This study found a high frequency of SARS at hospital admission. SARS-CoV-2 is known to infect airway epithelial cells or immune cells by attaching to the ACE2 receptor, causing clinical manifestations such as SARS, pneumonia, cytokine storms, and disseminated intravascular coagulation. The entrance and consequent replication of virus cells cause generalized impairments to epithelial tissues, increasing its permeability and accumulating protein-rich fluids in the alveolar and interstitial space. Cytokine storms are excessive releases of pro-inflammatory cytokines, which can cause fibrosis, diffuse alveolar damage, progressive respiratory insufficiency, and multiple organ failure (14). By mid-September 2021, Brazil had already reported approximately 1,775,816 cases of SARS caused by COVID-19, of which 32.2% progressed to death (15).

Clinically, COVID-19 manifests initially as an asymptomatic phase of silent viral replication, usually beginning on the fifth day after infection. Primary symptoms are mainly fever (88.7%), cough (57.6%), and dyspnea (45.6%). Other frequent symptoms are malaise (29.6%), fatigue (28.2%), neurological symptoms (20.8%), myalgia (16.9%), headache, diarrhea, and anosmia. Five to seven days after symptoms begin, viral replication decreases. However, some patients may enter the second phase, within 7 to 10 days, which is physiologically associated with immune reaction, mediated by cytokine release. In these cases, severe patients have SARS and/or multiple organ dysfunction; they may need ICU stays and are prone to having secondary infections (16). This corroborates our findings, as ICU stays occurred mostly among patients with lower SpO_2 values.

Most of the sample were older adults like in other studies (17, 18, 19), who had a greater likelihood of ICU stay and mortality. Aging has been associated with worse outcomes in COVID-19 infections, as advancing age can increase chronic disease burden and cause physiopathological changes in the respiratory system. Older adults have a declined capacity to depurate inhaled particles in small airways and fewer cilia and hair cells. These changes take place during the aging process, along with a linear increase in nasal cavity volume and a decrease in age-dependent nasal resistance. When invaded by microorganisms, toll-like receptors (TLR) in antigen-presenting cells recognize the strategic segment of microbes and induce the secretion of different cytokines, synchronizing effector cells to defend the host. However, this mechanism is seemingly impaired in older adults due to immunosenescence. Meanwhile, there is a positive TLR-4 regulation in dendritic cells derived from monocytes, which apparently favors inflammation (20).

ICU stay increased the risk of mortality, and the prevalence of patients needing intensive support (47.8%) was similar to a study by García-Posada et al.[19], who observed that 47.8% (n = 100) patients stayed in ICU in a sample of 219 individuals with COVID-19. Lower SpO_2 levels at hospital admission contributed to ICU stay and were related to mortality. Mejía et al. (21) demonstrated in their study with 369 patients at a public tertiary hospital in Peru that low SpO_2 levels (<90%) at hospital admission were predictive of mortality. They also found that the early identification of hypoxemia may direct the care given to patients with a suspicion of COVID-19 and provide timely access to oxygen therapy, decreasing the risks of persistent hypoxemia and consequent mortality rates. Hypoxemia can be silent (i.e., without simultaneously increasing respiratory effort), due to an imbalance between pulmonary ventilation and capillary blood flow (ventilation/perfusion), quickly causing the patients' clinical deterioration. The main contributing mechanisms may be local interstitial edema, pulmonary atelectasis, and vascular microthrombi formation, due to impaired ACE2-expressing capillary endothelial cells in the lungs in response to severe inflammations and endothelial lesions (22).

In this study, the diabetes, either alone or in combination with hypertension, was associated with ICU stays. Diabetes and the degree of individual hyperglycemia are seemingly associated with the severity of COVID-19 infection and increased risk of mortality. It is suggested that in human monocytes, high glucose levels directly increase

SARS-Cov-2 replication, and glycolysis maintains virus replication with mitochondrial production of reactive oxygen species and activation of hypoxia--inducible factor 1-alpha. Moreover, type 2 diabetes mellitus causes an immune system dysfunction equivalent to rapid aging, worsening the prognosis in COVID-19 patients and requiring high doses of exogenous insulin for glycemic control, which is related to increased inflammatory cytokine levels. ACE2 receptors may be also expressed in pancreatic islet cells, damaging the endocrine pancreas, and contributing to hyperglycemia (23).

There was a greater prevalence of overweight and obesity in hospitalized individuals. Even though the study did not demonstrate it, the relationship between obesity and unfavorable clinical outcomes is recognized in hospitalized COVID-19 patients (24). Although no significant difference was found between assessed outcomes in adults with normal BMI and with obesity, The mean BMI in the study population was higher than 30 kg/m^2, which is like data in the literature. Obesity is present in COVID-19 patients, especially in more severe cases, with worse prognoses, longer lengths of stay, greater need for mechanical ventilation, and early start of renal replacement therapy (25, 26). Some limitations in our study – e.g., unrecorded weight and height in one third of the sample's medical records and care and biosafety precautions at the beginning of the pandemic (8) –may have hindered more reliable nutritional diagnoses in the study population.

The prevalence of renal dysfunction in hospitalized COVID-19 patients was like the reported by Legrand et al. (27). In this study, impaired renal function was related to the need for ICU stay and increased risk of mortality. Renal lesions in SARS--CoV-2 infection are a complex mechanism that may involve factors such as tubular injury secondary to local inflammation, tissue hypoxia/hypoperfusion, drug-induced nephrotoxicity (e.g., antibiotics and antivirals), rhabdomyolysis, vascular injury with endothelial inflammation, microthrombi formation, and thrombotic microangiopathy, glomerular injury with the occurrence of collapsing glomerulopathy and glomerulonephritis, tissue injury with severe interstitial nephritis and immune cell infiltration, and interstitial edema (27). Besides impaired renal function, leukocytosis, thrombocytopenia, lymphopenia, and high ferritin levels were also related to the need for ICU stay and/or mortality. A meta-analysis identified that severe and fatal COVID-19 patients had significantly higher leukocyte counts and lower lymphocyte and platelet counts than non-severe patients and survivors (28).

Inflammation biomarkers, cardiac and muscle lesions, hepatic and renal functions, and coagulation measures were also significantly higher in severe and fatal COVID-19 patients (28, 20). This corroborates the findings in this study, as urea, creatinine, LDH, CRP, CPK, and troponin T values were significantly higher in patients who died. It is recommended that leukocyte, lymphocyte, and platelet count and serum levels of ferritin be monitored as markers of progression to more severe forms of the disease (28). In contrast with CRP levels, patients who died had significantly lower levels of albumin. Hypoalbuminemia is common in COVID-19 patients and is more associated with the severity of the disease (29).

As demonstrated by other authors (17, 30), individuals who did not survive had significantly higher D-dimer levels than survivors. Furthermore, D-dimer levels in the first 24 hours were higher in patients who needed ICU stays, indicating that severe patients have higher levels of this marker. Hosseinzadeh and collaborators (31) demonstrated that d-dimer values > 1.12 µg/mL in the initial phase of COVID-19 infection, that is, in the first 24 hours of hospitalization, can independently predict a more severe form of the disease, with greater pulmonary involvement and risk of death, corroborating our findings. Increased D-dimer levels are found in viremia and cytokine storm syndrome, in which the increase in pro-inflammatory cytokines (IL-2, IL-6, IL-8, IL-17, TNF-) is inadequately modulated by inflammatory factors that overload the coagulation cascade. Hypoxia alone activates the signaling pathway of the hypoxia-induced transcription factor, predisposing to thrombotic events (30).

In this sturdy, advanced age was a negative prognosis factor, with evidence that older adults

were at a greater risk of ICU stay and mortality. It is suggested that lower SpO2 values may timely identify those patients who benefited from early supplemental oxygen therapy, reducing the risk of mortality. Patients with renal dysfunction, alteration of coagulation factors and increase in inflammatory markers in the first 24 hours of hospitalization were more tolerant to hospitalization for UTI and death. Higher BMI was related to survival, probably because most subjects in this study were older adults, and patients with higher BMI may have better functional reserve to deal with inflammatory diseases, which impose greater metabolic demands.

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The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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