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Original Article

Nutritional factors associated with mortality in hospitalized patients with COVID-19

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SUMMARY

Background & aims: Malnutrition is a risk factor that can lead to diminished physical and mental function and impaired clinical outcome from diseases. This study was performed to investigate the influence of nutritional characteristics, age and the presence of pre-comorbidities in hospital mortality or medical discharge in a sample of hospitalized patients with COVID-19.

Methods: This historical cohort study was conducted in adults and elderly patients with COVID-19 who were admitted to a nursing ward at the University Hospital of Brasília (Brazil). Data regarding demographics, comorbidities, laboratory parameters, nutritional characteristics (NRS 2002, SARC-F, BMI) and discharge or death were retrospectively extracted from medical records. Differences in each group (in-hospital mortality or discharge) were assessed using unpaired Student's t test for continuous variables, or Pearson Chi-square tests for categorical data.

Results: A total of 222 patients with COVID-19 were enrolled in this study. Nutritional risk and sarcopenia risk were higher in patients who died compared to patients who were discharged (3.55 ± 1.30 vs 2.96 ± 1.30 ; $p = 0.005$, 6.81 ± 1.84 vs 4.96 ± 2.95 ; $p < 0.001$, respectively). BMI, albumin, and total protein were lower in mortality group than in the discharge group (25.10 ± 5.46 vs 27.82 ± 6.76 ; $p = 0.009$, 2.81 ± 0.62 vs 3.27 ± 0.53 ; $p < 0.001$, 6.08 ± 0.87 vs 6.48 ± 0.86 ; $p = 0.007$, respectively). The mean age

Abbreviations: BMI, Body Mass Index.

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between groups was also different with a higher age in the mortality group (70.24 ± 16.23) than in the discharge group (60.54 ± 16.57).

Conclusions: Uses of validated tools to identify risk for malnutrition and sarcopenia would be beneficial in hospitalized patients with COVID-19 in order to optimize the treatment between them. Published by Elsevier Ltd on behalf of European Society for Clinical Nutrition and Metabolism. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first detected in China in 2019 and rapidly spread to other countries [1].

When SARS-CoV-2 infects the respiratory tract, it can cause mild respiratory infections or severe acute respiratory syndrome with consequent inflammatory responses [2]. Severe COVID-19 is characterized by hyper-inflammation, cytokine storm, acute respiratory distress syndrome (ARDS), damage to the lung, heart and kidneys.

In relation to muscle, hyper-inflammation increases reactive oxygen species (ROS) generation which activates the production of pro-inflammatory cytokines in the muscular tissue causing atrophy and functional decline in the muscle [3,4].

Patients aged over 60 years old and those with underlying conditions (such as hypertension, diabetes, cardiovascular disease, and chronic respiratory disease) are at a higher risk of death and a matter of great concern in clinical management [3,4]. Malnutrition is another risk factor which can lead to diminished physical and mental function and impaired clinical outcome from disease [5].

Besides malnutrition, the other nutritional disorder which has been associated with adverse outcomes is sarcopenia [6]. It is a progressive and generalized skeletal muscle disorder characterized by loss of muscle and strength [7]. Sarcopenia is not limited to peripheral skeletal muscles. The loss of muscular tissue is seen in the respiratory muscles, resulting in pulmonary function disorders and infections [8].

This study was performed to investigate the influence of nutritional characteristics (nutritional risk, sarcopenia risk, laboratory data), age and the presence of pre-comorbidities on in-hospital mortality or medical discharge in a sample of patients with COVID-19 hospitalized in a University Hospital in Brasilia (Brazil).

2. Materials and methods

2.1. Design, setting and population

This historical cohort study was conducted at the University Hospital of Brasilia (Brazil) in adults and elderly patients admitted to the nursing ward of the unit of management for severe acute respiratory syndrome, from August, 2020 to April, 2021. All the data was collected from the medical records of each patient. The diagnosis of COVID-19 was defined by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test for the SARS-CoV-2 on nasopharyngeal swabs or chest computerized tomography scans characterized by ground-glass opacities (typical pattern for the infection by SARS-CoV-2). We included only patients who were still in the period of respiratory isolation which was considered as 15 days from the positive diagnosis. Other patients who were excluded from the sample, were patients who escaped from the hospital, patients who had no Nutritional Risk Screening (NRS) registered in their medical records or if the NRS had been made using remote data or if it had been

made after 48 h from the admission. We also excluded patients who were already in-hospital because of other disease and were infected by COVID-19 in the hospital. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. The project was authorized by the Research Ethics Committee of University of Brasília, Brazil, School of Medicine.

2.2. Data collection

Data regarding demographics, comorbidities, laboratory parameters, nutritional characteristics and discharge or death were retrospectively extracted from medical records.

Nutritional risk screening was performed at the point of hospital admission by experienced dietitians according to the NRS-2002. This score assesses the BMI status, weight loss history and nutritional intake (0–3 points) and the severity of the acute disease (0–3 points), with a total score ranging from 0 to 7, and an additional point was added for patients aged 70 or older. Patients were classified as “at nutritional risk” with a score of ≥ 3 , whereas a score < 3 indicated no nutritional risk [9].

Risk of sarcopenia was assessed in elderly patients using the SARC-F questionnaire during hospital admission. A total score of 4 or more indicated an increased risk of sarcopenia [10].

Laboratory variables were determined by standard clinical chemical methods in the hospital by routine blood test. We collected those variables on the same day or the closest date of the assessment of NRS for each patient. The exams collected were: albumin, globulin, total protein, lymphocytes and vitamin D.

Patients are considered elderly who are 60 years old or more according to World Health Organization (WHO) [11]. Body mass index (BMI) was calculated ($\text{weight}/\text{height}^2$) and categorized for adults (< 60 years-old) as described by WHO [12]: underweight BMI $< 18.5 \text{ kg/m}^2$, normal weight BMI $18.5\text{--}24.9 \text{ kg/m}^2$, overweight BMI $25\text{--}29.9 \text{ kg/m}^2$, obesity BMI $\geq 30 \text{ kg/m}^2$. For elderly (≥ 60 years-old), BMI was categorized according to Pan American Health Organization [13]: underweight BMI $\leq 23 \text{ kg/m}^2$, normal weight BMI $23.1\text{--}27.9 \text{ kg/m}^2$, overweight BMI $28\text{--}29.9 \text{ kg/m}^2$, obesity BMI $\geq 30 \text{ kg/m}^2$.

The most common chronic diseases between the subjects were collected and then categorized as diabetes mellitus (DM), hypertension, chronic kidney disease (CKD) and coronary disease. The patients were also grouped according to the number of chronic diseases which they had.

2.3. Statistical analysis

Descriptive analyses were expressed using proportion or means with standard deviations (SD) for sociodemographic features (gender, age), tobacco use, alcoholism, presence of chronic diseases and nutritional features (nutritional state according to BMI, NRS, SARC-F, albumin, globulin, total protein, lymphocytes, and vitamin D).

Continuous variables were expressed as the mean \pm SD (standard deviation) or SE (standard error) and categorical data as percentages. The variables were categorized in two groups according to deaths or discharge. Differences in each group were assessed using unpaired Student's *t* tests for continuous variables or Pearson Chi-square tests for categorical data. An adjusted analysis (controlling by age, BMI and NRS) was assessed using a one-way analysis of covariance (ANCOVA) with group (Mortality and Discharge) as between subject factor and age, BMI and NRS as covariate. Analyses were performed for the entire sample and also stratified by age. Results with *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software version 22.0 (IBM, USA).

3. Results

A total of 222 patients with COVID-19 were enrolled in the study. Fig. 1 shows patients flow in the study. Data for laboratory exams were not available for all patients. We collected 191 data from albumin, 188 from globulin and total protein, 221 from lymphocytes and 34 from vitamin D. Furthermore, SARC-F data was available for only 131 patients.

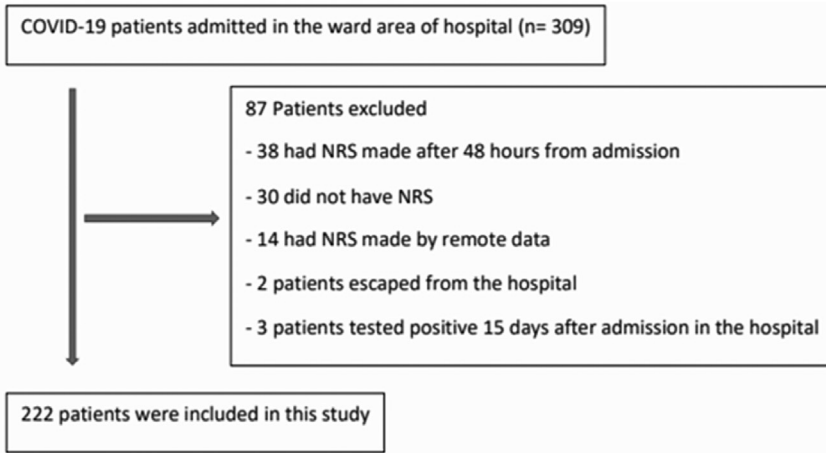


Fig. 1. Patients process flowchart.

Table 1

Social factors, chronic diseases, and nutritional features among the total sample.

Characteristics	Total n = 222
Men/Women	125 (56.3%)/97 (43.7%)
<60 years/≥60 years	86 (38.7%)/136 (61.3%)
Tobacco use/Alcoholism	63 (28.4%)/27(12.2%)
Hypertension	138 (62.2%)
Diabetes	91 (41.0%)
Chronic kidney disease	73 (32.9%)
Coronary disease	65 (29.3%)
One/two or more chronic diseases	54 (24.3%)/146 (65.8%)
No chronic disease	22 (9.9%)
Underweight	45 (20.3%)
Normal weight	81 (36.5%)
Overweight	36 (16.2%)
Obesity	60 (27.0%)
NRS <3/≥3	85 (38.3%)/137 (61.7%)
SARC-F ^a <4/≥4	27 (26.5%)/75 (73.5%) [n = 102]

NRS: Nutritional Risk Screening.

^a Data were not fully available in all patients: n values in brackets within the table depicts the number of patients with available data.

The mean age of the subjects was 62.8 and most were male (56.3%) and elderly (61.3%). The most common chronic diseases were hypertension (62.2%) followed by diabetes (41%). Only 9.9% of the subjects did not have any chronic disease (Table 1).

Other chronic diseases less frequently encountered were cancer (4.9%), hyperthyroidism or hypothyroidism (6.7%), related to nervous system (dementia, Parkinson, etc.) (14.9%), infection by Human Immunodeficiency Virus (HIV) (0.9%), liver disease (2.2%), asthma (5.9%), pulmonary obstructive chronic disease (1.8%), dyslipidemia (1.8%), autoimmune diseases (0.9%) and others (pancreatitis, leprosy, anemia, gout, arthrosis, prostatic hyperplasia) (10.4%) (data not shown).

The greater percentage of the patients was classified as normal weight (36.5%). However, when adding overweight and obese, the percentage correspond to almost half of the sample (43.2%). Nevertheless, the majority of the subjects had nutritional risk (61.7%). (Table 1).

Regarding clinical outcome, 23% of patients died (n = 51) e 77% were discharged (n = 171). The mean age between groups was different and statistically significant (p < 0.001) with a higher age in

Table 2

Comparison of nutritional features among subjects hospitalized due to COVID-19 with criteria for in-hospital mortality or medical discharge.

Characteristics	Mortality (n = 51)	Discharge (n = 171)	p	Total
Age	70.24 (16.23)	60.54 (16.57)	<0.001	62.77 ± 16.96
BMI (kg/m ²)	25.10 ± 5.46	27.82 ± 6.76	0.009	27.2 ± 6.6
Adult	24.49 ± 6.81	29.37 ± 7.93	0.143	28.9 ± 7.9
Elderly	25.01 ± 5.17	26.57 ± 5.38	0.019	26.1 ± 5.3
NRS score	3.55 ± 1.30	2.96 ± 1.30	0.005	3.1 ± 1.3
Adult	3.40 ± 1.35	2.62 ± 1.31	0.08	2.7 ± 1.3
Elderly	3.59 ± 1.30	3.24 ± 1.24	0.146	3.3 ± 1.3
SARC-F ^a	6.71 ± 2.05 [n = 35]	4.53 ± 2.85 [n = 96]	<0.001	5.11 ± 2.83
Adult	5.67 ± 4.16	3.38 ± 2.25	0.137	3.62 ± 2.50
Elderly	6.81 ± 1.84	4.96 ± 3.95	0.001	5.51 ± 2.78
Albumin (g/L) ^a	2.81 ± 0.62 [n = 48]	3.27 ± 0.53 [n = 143]	<0.001	3.1 ± 0.6
Adult	2.62 ± 0.66 [n = 10]	3.37 ± 0.51 [n = 62]	<0.001	3.3 ± 0.6
Elderly	2.86 ± 0.61 [n = 38]	3.19 ± 0.54 [n = 81]	0.004	3.1 ± 0.6
Globulin (g/dL) ^a	3.27 ± 0.72 [n = 48]	3.22 ± 0.67 [n = 140]	0.671	3.2 ± 0.7
Adult	3.37 ± 1.10 [n = 10]	3.43 ± 0.77 [n = 62]	0.837	3.4 ± 0.8
Elderly	3.24 ± 0.61 [n = 38]	3.05 ± 0.54 [n = 78]	0.092	3.1 ± 0.6
Total protein (g/dL) ^a	6.08 ± 0.87 [n = 48]	6.48 ± 0.86 [n = 140]	0.007	6.4 ± 0.9
Adult	5.99 ± 0.89 [n = 10]	6.80 ± 0.93 [n = 62]	0.013	6.7 ± 1.0
Elderly	6.10 ± 0.88 [n = 38]	6.22 ± 0.71 [n = 78]	0.44	6.2 ± 0.8
Lymphocytes (cells/mm ³) ^a	1286.3 ± 1968.8 [n = 50]	1266.6 ± 1021.3 [n = 171]	0.925	1271.1 ± 1292.0
Adult	1750.4 ± 2358.0 [n = 10]	1238.2 ± 647.9 [n = 76]	0.126	1297.7 ± 993.2
Elderly	1170.3 ± 1875.6 [n = 40]	1289.4 ± 1245.1 [n = 95]	0.666	1254.1 ± 1454.1
Vitamin D (ng/mL) ^a	18.85 ± 9.87 [n = 8]	24.07 ± 12.11 [n = 26]	0.277	22.8 ± 11.7
Adult	9.10 ± 0.00 [n = 1]	22.87 ± 13.07 [n = 11]	0.337	21.7 ± 13.1
Elderly	20.25 ± 9.77 [n = 7]	24.94 ± 11.75 [n = 15]	0.37	23.4 ± 11.2

Data are mean ± SD. NRS: Nutritional Risk Screening.

^a Data were not fully available in all patients: n values in brackets within the table depicts the number of patients with available data.

mortality (70.24 ± 16.23) than in discharge group (60.54 ± 16.57). **Table 2** presents the comparison of nutritional features among subjects hospitalized due to COVID-19 with criteria for in-hospital mortality or medical discharge for the entire sample and stratified by adult (<60 years old) and elderly (≥60 years old).

Nutritional risk and sarcopenia risk were statistically significant higher in patients who died compared to patients who were discharged (3.55 ± 1.30 vs 2.96 ± 1.30; p = 0.005, 6.71 ± 2.05 vs 4.53 ± 2.85; p < 0.001, respectively). Moreover, BMI, albumin, and total protein were lower in the mortality group than in the discharge group (25.10 ± 5.46 vs 27.82 ± 6.76; p = 0.009, 2.81 ± 0.62 vs 3.27 ± 0.53; p < 0.001, 6.08 ± 0.87 vs 6.48 ± 0.86; p = 0.007, respectively). Similar results were observed in age-stratified analyses even though some results have lost their statistical significance (**Table 2**).

Table 3

Comparison of nutritional features among subjects hospitalized due to COVID-19 with criteria for in-hospital mortality or medical discharge, adjusted by Age, BMI and Nutritional Risk Screening (NRS).

	Mortality Mean ^a (SE)	Discharge Mean ^a (SE)	p ^b
SARC-F	6.35 ± 0.43	4.66 ± 0.26	0.001
Albumin (g/L)	2.87 ± 0.08	3.25 ± 0.05	<0.001
Globulin (g/dL)	3.32 ± 0.10	3.20 ± 0.06	0.299
Total Protein (g/dL)	6.19 ± 0.12	6.44 ± 0.07	0.092
Lymphocytes (cells/mm ³)	1321.18 ± 189.99	1256.40 ± 100.44	0.767
Vitamin D (ng/mL)	17.93 ± 4.22	24.35 ± 2.28	0.198

^a Estimated marginal means adjusted by Age, BMI and NRS; SE: Standard error.

^b ANCOVA with group (Mortality and Discharge) as between factor and Age, BMI and NRS as covariates.

After adjusting for age, BMI and NRS, SARC-F score and albumin levels remained significantly different between the mortality and the discharge groups (Table 3).

Categorical variables between patients who died or were discharged are shown in Fig. 2. Gender and toxic habits such as tobacco use, and alcoholism did not have statistical differences according to clinical outcome. However, mortality rate was more prevalent in older patients than in adult patients (80.4% vs 19.6%; $p = 0.001$). Considering the presence of chronic diseases, chronic kidney disease had the most and statistically significant difference between mortality and discharge with more patients affected by this disease in the mortality group than in the medical discharge group (45.1% vs 29.2%; $p = 0.034$).

All the nutritional characteristics of the subjects were statistically significant for clinical outcomes. Nutritional risk was prevalent in patients who died compared to patients who did not have a nutritional risk (78.4% vs 21.6%; $p = 0.005$). The mortality group had more underweight and normal weight than overweight and obese patients (33.3%, 45.1% vs 7.8%, 13.7%; $p = 0.003$, respectively). However, there were an inverse and significant correlation between BMI and age (Pearson correlation = -0.249 ; $p < 0.001$) which indicates that old patients had lower BMI and could explain a higher mortality in underweight and normal weight patients.

4. Discussion

This study shows that patients who died due to covid-19 infection were older and had higher nutritional risk and sarcopenia risk as well as lower albumin and BMI values than patients who were discharged. Moreover, in the mortality group, there were more patients affected by CKD and more underweight and normal weight than overweight and obese patients.

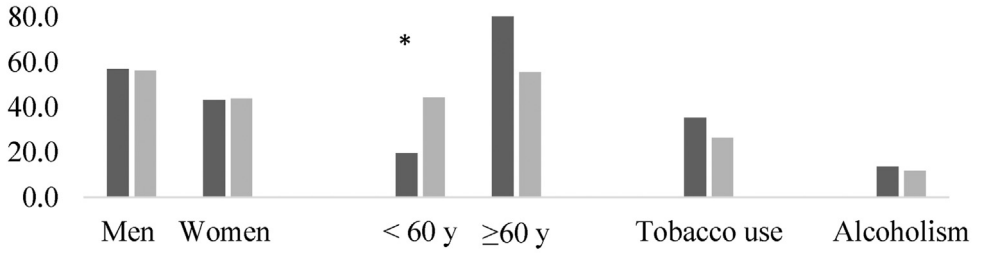
Patients who died had a mean age of 70.24 years old, which corresponded to 10 years more than patients who were discharged. In addition, in the mortality group, 80.4% were more than 60 years old. Riesgo et al. [14], studying the factors related with mortality in elderly with COVID-19, found an association between older age and mortality. In fact, old people experience the immunosenescence process which reduces the effectiveness of both the adaptive and innate immune responses to pathogens, and thus limiting survival [15]. Associated with this process, there is another common mechanism in older subjects called inflammaging. It is related to accumulation of senescent cells that can entail senescence associated secretory phenotype comprising proinflammatory cytokines which increase the inflammatory readiness in the aging organism, even without direct stimulation of the inflammatory process. All these mediators, associated with cytokine storms which can be seen in patients with COVID-19, leads to hyperinflammation and aggravates the multi-organ damage, leading to the acute respiratory distress syndrome (ARDS) and respiratory failure [16].

Another result related to inflamaging process and higher mortality in older patients, is the fact that 90% of these subjects had at least one comorbidity. The chronic low-grade inflammation is responsible for aging-related diseases including heart disease, malignancies, dementia, type 2 diabetes, obesity and arterial hypertension [16]. In this study, although it was not statistically significant, the mortality group had more patients with diabetes, hypertension and coronary disease than the discharge group. Moreover, the prevalence of comorbidities in this study was about 15% higher than other studies [17,18].

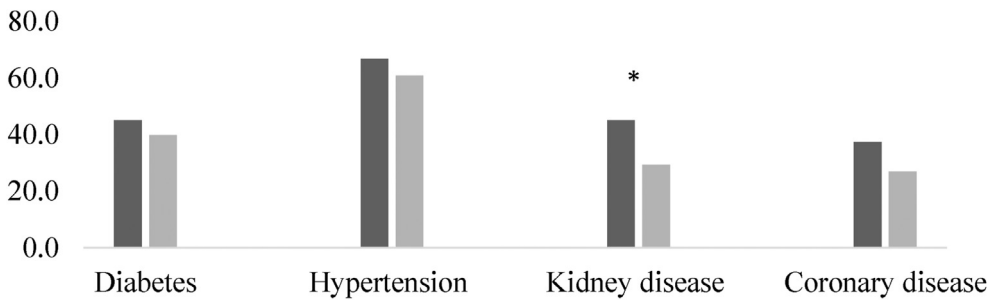
Among comorbidities, CKD was the only disease which had different prevalence between clinical outcomes, with more CKD patients in the mortality group. In a review, Pecly et al. [19] concluded that CKD seems to be associated with more adverse clinical outcomes, more severe disease, higher mortality, and poorer prognosis in patients with COVID-19 infection. Actually, besides lung involvement, kidney damage can be observed in patients with SARS-CoV-2 infection, leading to acute kidney injury (AKI). Therefore, patients with more severe kidney dysfunction upon admission were more susceptible to kidney function worsening during hospitalization [19].

Nutritional characteristics were seen to be important to define prognosis of patients infected by coronavirus SARS-CoV-2, considering that all of these features were worsened in patients who died. In our study, 78.4% of patients who died were classified as at risk of undernutrition according to NRS 2002. NRS score was associated with the risk of mortality in patients with COVID-19 in other studies [20,21]. In addition, there is scientific evidence that NRS-2002 has an excellent sensitivity in identifying

A) Sociodemographic features, toxic habits



B) Chronic diseases



C) Nutritional features

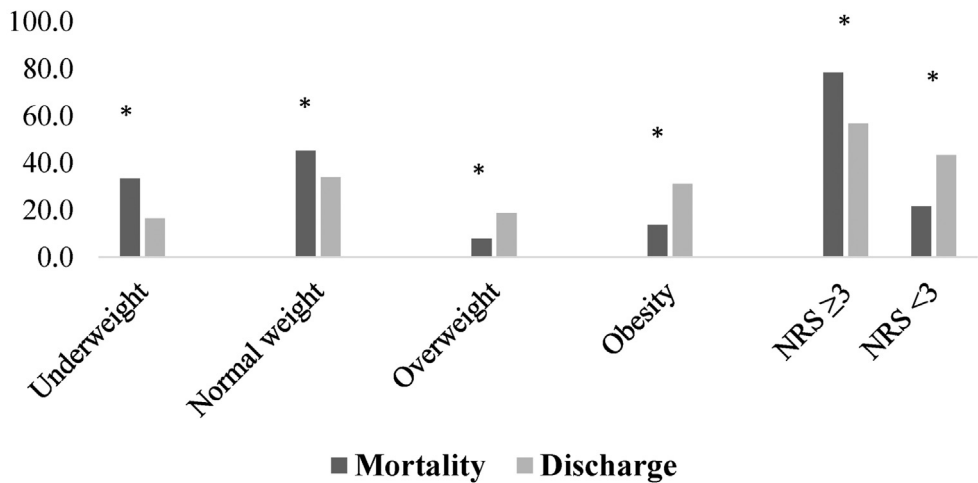


Fig. 2. Comparison of categorical variables among subjects hospitalized due to COVID-19 with criteria for in-hospital mortality or medical discharge. *Compared with mortality and discharge, $p < 0.05$.

patients with COVID-19 with poor clinical outcomes and is associated with length of hospitalization [22,23] and with an increased risk of loss of appetite [21–23].

In this study, the score obtained with SARC-F in the mortality group was higher than in the discharge group (6.81 ± 1.84 vs 4.96 ± 2.95 , respectively) although the mean of total sample was more than 4 (5.5 ± 2.8) which is the cutting point of classifying them as at risk for sarcopenia. This result can be explained by the higher proportion of the elderly in our sample. Similarly, Riesgo et al. [14] found a higher proportion of elderly patients with COVID-19 at risk of sarcopenia in the mortality group. A meta-analysis showed that sarcopenia was associated with increased severity of COVID-19 infection [24].

Another finding in nutritional features is lower albumin levels between deceased patients even after adjusted for age, BMI and NRS. It is important to note that for those who were discharged, the mean value of albumin was also low as. Similar result was presented in the research of Alikiaii et al. [21]. In fact, the synthesis of acute-phase proteins such as C-reactive protein, which is a common reaction seen in infections, requires the consumption of albumin and even muscle protein [25].

BMI is the other nutritional characteristic which has demonstrated to be different between clinical outcomes with mean value lower in the mortality group than the discharge group and a higher proportion of overweight and obese patients who were discharged. This result is controversial compared to other studies [26,27] and could be explained by the inverse correlation of BMI and age. The majority of patients who died were elderly and had a lower BMI. This fact indicates that age is more important than BMI to define risk of mortality in this population.

This study had some limitations. Firstly, it was conducted in a single center with a relatively small number of patients and with heterogenous clinical features between outcomes and possible unmeasured confounders. Secondly, we analyzed only patients who were admitted in ward areas and who died or who were discharged, but we did not collect information about other clinical outcomes and evolution of COVID-19 to more severe forms. In addition, we did not gather information about relocation to the intensive care unit and we did not know about outcomes after discharge. About the presence of comorbidities, we could not control them because almost 100% of patients had at least one comorbidity, which would impair the analysis. Finally, some data such as SARC-F and vitamin D were not possible to be collected to all patients because they were not available in medical records. Despite its limitations, this study controlled the age which is the strongest predictor of mortality and contributed to gather information about characteristics associated with poor prognosis in patients affected by coronavirus.

Considering the deleterious consequences of malnutrition, the use of validated tools should be encouraged in order to identify noncritically ill patients hospitalized for COVID at risk for malnutrition. Finally, uses of other nutritional parameters such as sarcopenia risk would be beneficial because the elderly are the group most affected and most at risk of developing the severe forms of the disease and presented a higher risk of mortality.

Statement of authorship

CL Silva and TMM Sousa conceptualized the study; JBS Junior and TMM Sousa collected the data; EY Nakano performed the statistical analysis; CL Silva drafted the original manuscript; all authors reviewed and edited the final manuscript.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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