

# High neutrophil-to-lymphocyte ratio at intensive care unit admission is associated with nutrition risk in patients with COVID-19

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## Abstract

**Background:** Inflammation plays a crucial role in nutrition status and can be useful in early nutrition risk screening of patients during the coronavirus disease 2019 (COVID-19) pandemic. Thus, this study aimed to assess the association between systemic inflammatory markers and nutrition risk tools in intensive care unit (ICU) patients with COVID-19.

**Methods:** Patients with confirmed COVID-19 and ICU admission were enrolled in a retrospective, observational, cross-sectional study. The medians of C-reactive protein (CRP;  $\geq 13.8$  mg/dl) and the neutrophil-to-lymphocyte ratio (NLR;  $\geq 12.6$ ) upon admission were used to dichotomize patients.

**Results:** Of the 73 patients, 63% were men; the average age was 56 years, and the median length of hospital stay was 10 (25th: 4; 75th: 17) days. When nutrition risk screening tools were used, 85% were at risk according to Nutritional Risk Screening ( $\geq 3$  points), whereas 42% had high risk according to the Modified Nutrition Risk in the Critically Ill (mNUTRIC;  $\geq 5$  points), and 57% were moderately or severely malnourished according to the Subjective Global Assessment (B or C). Mortality was higher in the group with NLR  $\geq 12.6$  than in the group with NLR  $< 12.6$ , with no difference between CRP groups. A significant association was found only between NLR and mNUTRIC, even when adjusted by sex, age, and body mass index (odds ratio, 1.36; 95% CI, 1.06–1.76;  $P = 0.016$ ), but not between CRP and nutrition risk.

**Conclusion:** Although the inflammatory marker CRP is the most used in hospital clinical practice, we found that only NLR was associated with nutrition risk (NUTRIC score).

## KEYWORDS

COVID-19, ICU, inflammation, nutrition status

## CLINICAL RELEVANCY STATEMENT

Inflammation plays a crucial role in nutrition status and clinical outcomes and can be useful in early nutrition risk screening of patients during the coronavirus disease 2019 (COVID-19) pandemic. Considering that chronic disease increases COVID-19-induced

complications, that the mortality rate of this study is 50.6% of patients, and that inflammation is critical to nutrition status, our study highlights the importance of evaluating the neutrophil-to-lymphocyte ratio as a key marker in the screening of nutrition risk in the intensive care unit in patients hospitalized with COVID-19.

## INTRODUCTION

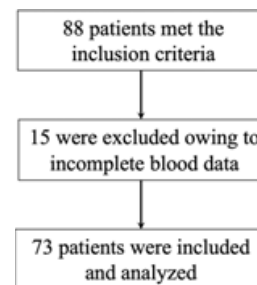
The World Health Organization (WHO) has named coronavirus disease 2019 (COVID-19) the disease caused by SARS-Cov-2. COVID-19 was declared a pandemic in March 2020 because of its high degree of infectiousness and has become a global health threat.<sup>1</sup> The virus spreads via droplets and aerosols released through the airways and is transmitted directly by contact or by air, with an incubation period of 2–14 days.<sup>2–4</sup> Although the most severe forms of COVID-19 have been described at all ages, several studies suggest that older patients and individuals with comorbidities have higher mortality rates.<sup>5–8</sup>

Invasion and replication of the SARS-Cov-2 virus in host cells promote cell damage that induces pyroptosis, stimulating a high degree of local inflammation and increased secretion of proinflammatory cytokines at the systemic level.<sup>9,10</sup> In more-severe cases, there is a higher concentration of inflammatory cytokines caused by hypersensitization of the immune system in response to viral infection and secondary infections.<sup>11</sup> It is evident that inflammation plays a crucial role in clinical outcomes in patients with COVID-19.<sup>10</sup> Thus, the assessment of severity markers, such as D-dimer, C-reactive protein (CRP), ferritin, and the neutrophil-to-lymphocyte ratio (NLR), are important in the screening and monitoring of clinical outcomes.<sup>12</sup>

Likewise, considering the relationship between the elevated systemic inflammatory state and protein catabolism in intensive care unit (ICU) patients, nutrition assessment and therapy are fundamental parts of the comprehensive and multiprofessional care of patients who are critically ill with COVID-19, given the positive association between high nutrition risk and worse clinical outcomes.<sup>13–15</sup> Early assessment of nutrition status is essential for producing and executing therapeutic care plans, avoiding the worsening of nutrition status, and improving clinical outcomes.<sup>16,17</sup> However, because of the heterogeneity of the clinical profiles of patients who are critically ill with COVID-19 and the metabolic changes that affect them, little is known about the use of existing nutrition risk assessment instruments validated for the general ICU public.<sup>18</sup>

Hu et al suggested that all ICU patients with COVID-19 should be screened early for nutrition risk by using validated tools, including the Nutritional Risk Screening (NRS) or Modified Nutrition Risk in the Critically Ill (mNUTRIC).<sup>19</sup> In addition, nutrition assessment tools have been suggested, such as the Subjective Global Assessment (SGA) and the Global Leadership Initiative on Malnutrition (GLIM).<sup>20</sup> Zhang et al used the mNUTRIC to screen nutrition risk in patients who are critically ill with COVID-19 and observed a strong relationship between high nutrition risk and mortality.<sup>18</sup>

Therefore, this study aimed to assess the association between systemic inflammatory markers and nutrition risk tools in ICU patients with COVID-19. Our hypothesis is that NLR and CRP are associated with the NRS, SGA, and mNUTRIC instruments and thus can be useful in clinical practice in the nutrition screening of patients who are critically ill with COVID-19.



**FIGURE 1** Participant flowchart

## METHODS

### Study design and participants

This was a retrospective, observational cross-sectional study conducted at a university hospital in the midwestern region of Brazil. This study was approved by the Research Ethics Committee of Hospital das Clínicas, Universidade Federal de Goiás (number 4.381.491).

The study included patients with suspected COVID-19 who were in critical condition, admitted to ICUs, 18 years or older, of both sexes. The following were excluded: patients with negative results in a reverse transcriptase–polymerase chain reaction test and those who did not have the available data on blood concentrations of CRP or white blood cell counts.

A convenience sample was established from March 2020 to October 2020, in which 88 patients who met the inclusion criteria were selected. Of these, 15 were excluded because their medical records contained incomplete data. Thus, 73 patients were included and analyzed (Figure 1).

### Data collection

The information was collected from medical records during the consultations performed at the surgical ICU and COVID-19 ICU. Data from the first 48 h of admission to the ICU were used.

Sociodemographic data (sex and age), anthropometric data (body weight and height), nutrition data (NRS 2002 and SGA), clinical data (length of ICU stays and mortality), presence of comorbidities (cancer, chronic obstructive pulmonary disease, cardiac insufficiency, chronic kidney disease, obesity, type 2 diabetes mellitus, and systemic arterial hypertension), prognostic indexes (Acute Physiology and Chronic Health Evaluation II [APACHE II],<sup>21</sup> Sepsis-Related Organ Failure Assessment [SOFA],<sup>22</sup> and mNUTRIC),<sup>23</sup> type of ventilation during hospitalization (mechanical ventilation [MV]), blood CRP concentrations, neutrophil and lymphocyte count, and D-dimer levels were collected.

To obtain NLR, the absolute blood neutrophil count was calculated by adding the rod-shaped and segmented neutrophils and was then divided by the absolute blood lymphocyte count. The biochemical method used to quantify serum concentrations of neutrophils and lymphocytes was the CELL-DYN Ruby automated hematology analyzer and microscopy. CRP concentrations were quantified by the biochemical immunoturbidimetric method.

In assessing the nutrition status, the body mass index (BMI) was used, dividing body weight (kilograms) by height (meters) squared.<sup>24–25</sup> Nutrition risk was obtained by using the NRS 2002<sup>26</sup>; patients with a score of <3 were considered as being not at nutrition risk, and those with a score of  $\geq 3$  were considered as being at nutrition risk. In addition, the mNUTRIC tool,<sup>27</sup> which excludes interleukin 6 (IL-6) levels, was also used to identify critically ill patients at risk of unfavorable outcomes that can be modified by aggressive nutrition intervention, in which scores of <4 were considered predictors of low risk and scores of  $\geq 5$ , predictors of high risk. Regarding the nutrition diagnosis, the SGA<sup>28</sup> result was taken into account as follows: nourished (A), moderately malnourished (B), and severely malnourished (C).<sup>18–20</sup> The SGA is a tool routinely performed by a trained nutritionist in patients who are critically ill with COVID-19 and in the hospital.

The patients were dichotomized by using the sample median results for NLR and CRP concentrations, because there is still no consensus in the literature on these cutoff points in patients critically ill with COVID-19. The results were 12.6 for NLR and 13.8 mg/dl for CRP. NLR values above or equal to the median (12.6) were classified as indicators of high inflammation. Likewise, CRP concentrations above or equal to the median (13.8 mg/dl) were classified as indicators of high inflammation.

## Statistical analyses

Descriptive statistical analysis was performed with a cutoff point of 12.6 for NLR and 13.8 mg/dl for CRP. The data were tabulated in an Excel spreadsheet, and then, the normality test was performed by using the Kolmogorov-Smirnov test. Normal variables were presented as mean  $\pm$  SD and nonnormal values as median, minimum, and maximum.

Categorical data were presented as absolute (*n*) and relative (%) values. For comparisons of means, Student *t*-test was performed in the presence of normally distributed data, and the Mann-Whitney *U* test was performed for data that did not show a normal distribution. Logistic regression analysis was performed to verify the presence of an association between the variables mNUTRIC, NRS, and SGA (continuous data as independent variables) and the systemic inflammation markers NLR and CRP (categorical data as a dependent variable).

The variables related to nutrition status were analyzed as continuous numbers, and the data were presented in the crude model and adjusted for age, BMI, and sex (model 1). The regression results are presented as odds ratios (ORs) and 95% CIs. The MedCalc software (version 11.1.1.0) was used for all analyses, and results were considered statistically significant at  $P < 0.05$ .

## RESULTS

The sample ( $n = 73$ ) had a mean age of 56 years and was mostly composed of men (63%). The median number of days in the COVID-19 ICU was 10 (25th percentile: 4; 75th percentile: 17), and mortality was 50.6%. The most frequent comorbidity among patients was hypertension (49.3%), followed by obesity (41%) and diabetes (30%). The mean duration of MV was  $13.4 \pm 8.3$  days, the mean BMI was 29, and 23.3% of patients were obese (BMI  $\geq 30$ ).

Of the total, 50.6% of patients died during hospitalization, 85% presented nutrition risk with NRS  $\geq 3$ , 42% had high risk with NUTRIC  $\geq 5$ , and 57% were moderately or severely malnourished according to SGA (B or C).

When patients were dichotomized according to the medians of NLR and blood CRP concentration, higher mortality, longer MV in the first 24 h in the ICU, and higher APACHE, SOFA, mNUTRIC, and NRS scores were observed in patients with NLR  $\geq 12.6$ . In addition, those in the group with NLR  $\geq 12.6$  also had lower BMI when compared with that of patients with low NLR (<12.6) (Table 1). When patients were dichotomized according to CRP, differences between the two groups regarding the nutrition status variable SGA were found. However, it is interesting to note that severely malnourished patients were not observed in the group with CRP  $\geq 13.8$  mg/dl. Additionally, patients in the group with CRP  $\geq 13.8$  mg/dl tended to have higher BMI than those in the group with low CRP (Table 2).

In logistic association analyses, NLR was positively associated with mNUTRIC in the crude model and model 1 when adjusted for age, sex, and BMI (OR, 1.36; 95% CI, 1.06–1.76;  $P = 0.016$ ) (Table 3). However, CRP was not associated with any of the nutrition risk assessment variables (mNUTRIC, SGA, and NRS) (Table 4).

## DISCUSSION

Although the inflammatory marker CRP is the most used in hospital clinical practice, we found that only NLR was associated with nutrition risk (NUTRIC score), which may be important in determining nutrition risk in patients who are critically ill with COVID-19. One hypothesis for this result is that the mNUTRIC score evaluates in more detail variables of inflammation and disease severity when compared with the NRS and SGA tools, which evaluate predominantly nutrition variables.<sup>17,29</sup>

CRP was not associated with tools that screen for nutrition risk or nutrition assessment for the diagnosis of malnutrition (NRS and SGA, respectively). A possible explanation for this is that, according to Li and Chan, blood levels change rapidly because of various acute-phase factors related to infectious or inflammatory activity or tissue damage and are not necessarily associated with the immune response and nutrition risk, as NLR was shown to be in this study.<sup>30</sup> Although CRP participates in innate immunity, there are no reports of decreases in its values and participation in the reduction in the immune response.<sup>31</sup> In addition, according to Aguiar et al, CRP has a plasma half-life of 19 h and can remain high for several days, even in the absence of stimuli. For this

**TABLE 1** Data of patients admitted to the ICU according to NLR classification

Variables	NLR < 12.6 (n = 36)	NLR ≥ 12.6 (n = 36)	P
Sex (n = 72), n (%)			1.00
Male	23 (63.8)	22 (61.2)	
Female	13 (36.2)	14 (38.8)	
Age, mean ± SD, years	53.4 ± 15.0	58.4 ± 18.6	0.11
Length in ICU, median (25th–75th), days	6.5 (3.2–11.0)	12 (5–19.5)	0.34
Mortality (n = 72), n (%)			0.004*
Alive	24 (66.6)	11 (30.5)	
Died	12 (33.3)	25 (69.5)	
Comorbidities (n = 72), n (%)			0.66
Cancer	3 (8.3)	6 (16.6)	
COPD	5 (18.8)	7 (19.4)	
Insufficiency cardiac	3 (8.3)	4 (11.1)	
Chronic kidney disease	5 (18.8)	5 (18.8)	
Diabetes	12 (33.3)	10 (27.7)	
Obesity (BMI ≥ 30)	20 (55.5)	10 (27.7)	
Hypertension	18 (50.0)	18 (50.0)	
No	4 (11.1)	5 (18.8)	
APACHE II, mean ± SD, score	14.9 ± 9.7	22.1 ± 10.7	0.002*
SOFA, mean ± SD, score	5.4 ± 5.1	8.4 ± 4.7	0.01*
Mechanical ventilation (n = 72), n (%)			0.004*
No	25 (69.5)	13 (36.1)	
Yes	11 (30.5)	23 (63.9)	
Mechanical ventilation duration, mean ± SD, days	13.5 ± 8.9	13.3 ± 8.3	0.48
BMI, mean ± SD	30.6 ± 6.6	27.5 ± 5.9	0.02*
mNUTRIC, mean ± SD, score	3.4 ± 2.3	5.2 ± 2.5	0.002*
mNUTRIC (n = 72), n (%)			0.15
Low risk (1–4)	24 (66.6)	17 (47.3)	
High risk (≥5)	12 (33.7)	19 (52.7)	
Nutrition risk screening, mean ± SD, score	3.5 ± 1.2	4.1 ± 1.2	0.03*
Nutrition risk screening (n = 72), n (%)			0.47
No risk	6 (16.7)	3 (8.3)	
With risk	30 (83.3)	33 (91.7)	
Subjective Global Assessment (n = 72), n (%)			0.26
Well-nourished (A)	18 (50)	12 (33.3)	
Moderately malnourished (B)	17 (47.3)	21 (58.4)	
Severely malnourished (C)	1 (2.7)	3 (8.3)	
Biochemical analysis			
Hematocrit, mean ± SD, %	37.0 ± 8.2	37.4 ± 8.0	0.40
Hemoglobin, mean ± SD, g/dl	12.0 ± 2.7	12.1 ± 2.6	0.43
C-reactive protein, median (25th–75th), mg/dl	6.0 (3.0–12.0)	7.0 (4.5–21.0)	0.01*
D-dimer, median (25th–75th), ng/ml	610.0 (277–898)	820.0 (422–1528)	0.46
NLR, median (25th–75th)	11 (6–41.5)	31 (16–65.7)	<0.0001*

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; 25th, percentile 25th; 75th, percentile 75th; mNUTRIC, Modified Nutrition Risk in the Critically Ill; NLR, neutrophil-to-lymphocyte ratio; SOFA, Sepsis-Related Organ Failure Assessment.

\*P < 0.05 was considered as significant.

**TABLE 2** Data of patients admitted to the ICU according to CRP classification

Variables	CRP < 13.8 mg/dl (n = 36)	CRP ≥ 13.8 mg/dl (n = 37)	P
Sex (n = 73), n (%)			0.37
Male	25 (69.5)	21 (56.7)	
Female	11 (30.5)	16 (43.3)	
Age, mean ± SD, years	58.6 ± 16.3	53.4 ± 15.4	0.09
Length in ICU, median (25th–75th), days	8 (3.2–11)	12 (5–18.5)	0.40
Mortality (n = 73), n (%)			0.72
Alive	19 (52.7)	17 (46.0)	
Died	17 (47.3)	20 (54.0)	
Comorbidities (n = 73), n (%)			0.72
Cancer	5 (13.8)	4 (10.8)	
COPD	9 (25.0)	3 (8.1)	
Insufficiency cardiac	5 (13.8)	2 (5.4)	
Chronic kidney disease	5 (13.8)	5 (13.5)	
Diabetes	12 (33.3)	10 (27.0)	
Obesity (BMI ≥ 30)	14 (38.8)	16 (43.2)	
Hypertension	18 (50.0)	18 (48.6)	
No	5 (13.8)	4 (10.6)	
APACHE II, mean ± SD, score	17.9 ± 11.2	18.8 ± 10.5	0.36
SOFA, mean ± SD, score	6.3 ± 5.0	7.3 ± 5.2	0.21
Mechanical ventilation (n = 73), n (%)			1.00
No	36 (100)	36 (97.2)	
Yes	0 (0)	1 (2.8)	
Mechanical ventilation duration, mean ± SD, days	13.4 ± 8.5	13.4 ± 8.5	0.49
BMI, mean ± SD	27.9 ± 6.0	30.0 ± 6.6	0.07
mNUTRIC, mean ± SD, score	4.2 ± 2.9	4.3 ± 2.3	0.43
mNUTRIC (n = 73), n (%)			0.91
Low risk (1–4)	20 (55.5)	22 (59.4)	
High risk (≥5)	16 (44.5)	15 (40.6)	
Nutrition risk screening, mean ± SD, score	3.7 ± 1.4	3.9 ± 1.1	0.25
Nutrition risk screening (n = 73), n (%)			0.48
No risk	7 (19.4)	4 (10.8)	
With risk	29 (80.6)	33 (89.1)	
Subjective Global Assessment (n = 73), n (%)			0.02*
Well-nourished (A)	18 (50.0)	13 (35.2)	
Moderately malnourished (B)	14 (38.8)	24 (64.8)	
Severely malnourished (C)	4 (11.2)	0 (0)	
Biochemical analysis			
Hematocrit, mean ± SD, %	37.7 ± 7.0	36.8 ± 9.0	0.33
Hemoglobin, mean ± SD, g/dl	12.3 ± 2.3	12.0 ± 3.0	0.28
CRP, median (25th–75th), mg/dl	5 (2.7–7.2)	16 (6–24)	<0.0001*
D-dimer, median (25th–75th), ng/ml	407.5 (140–701.7)	898 (438.7–2154.2)	0.054
Neutrophil-to-lymphocyte ratio, median (25th–75th)	15.5 (7.7–48.5)	28 (12–47.7)	0.14

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; 25th, percentile 25th; 75th, percentile 75th; mNUTRIC, Modified Nutrition Risk in the Critically Ill; SOFA, Sepsis-Related Organ Failure Assessment.

\* $P < 0.05$  was considered as significant.

**TABLE 3** Association between NLR and nutrition risk variables in patients with COVID-19 admitted to the intensive care unit

Variables	OR (95% CI)	P
NLR × mNUTRIC		
Crude	1.34 (1.09–1.64)	0.005*
M1	1.36 (1.06–1.76)	0.016*
NLR × SGA		
Crude	1.95 (0.85–4.44)	0.11
M1	1.25 (0.46–3.36)	0.65
NLR × NRS		
Crude	1.47 (0.96–2.26)	0.07
M1	1.23 (0.77–1.97)	0.36

Note: NLR was entered as a categorical variable (dependent), and mNUTRIC, SGA, and NRS were entered as continuous variables (independent). M1: adjusted by age, body mass index, and sex.

Abbreviations: M1, model 1; mNUTRIC, Modified Nutrition Risk in the Critically Ill; NLR, neutrophil-to-lymphocyte ratio; NRS, Nutritional Risk Screening; OR, odds ratio; SGA, Subjective Global Assessment.

\*P < 0.05 was considered as significant.

**TABLE 4** Association between CRP and nutrition risk variables in patients with COVID-19 admitted to the intensive care unit

Variables	OR (95% CI)	P
CRP × mNUTRIC		
Crude	1.01 (0.84–1.21)	0.86
M1	1.18 (0.92–1.50)	0.17
CRP × SGA		
Crude	1.11 (0.50–2.44)	0.78
M1	1.84 (0.68–4.94)	0.22
CRP × NRS		
Crude	1.14 (0.78–1.67)	0.49
M1	1.45 (0.91–2.31)	0.11

Note: CRP was entered as a categorical variable (dependent), and mNUTRIC, SGA, and NRS were entered as continuous variables (independent). M1: adjusted by age, body mass index, and sex.

Abbreviations: CRP, C-reactive protein; M1, model 1; mNUTRIC, Modified Nutrition Risk in the Critically Ill; NRS, Nutritional Risk Screening; OR, odds ratio; SGA, Subjective Global Assessment.

reason, monitoring dosages over a period of days is more useful than isolated results.<sup>32</sup> In the present study, we did not find any severely malnourished patients in the group with CRP  $\geq$  13.8 mg/dl. Indeed, CRP levels are not linearly correlated with nutrition status,<sup>33</sup> suggesting that during high-grade inflammation, as in infection by COVID-19, the nutrition status may be modulated by other cytokines rather than by CRP levels. Considering that patients in the group with CRP  $\geq$  13.8 mg/dl tended to have higher BMI than those in the group with low CRP, overweight has been suggested to explain the absence of malnourished patients in the group with high inflammation when measured by CRP.

The inflammatory response plays a fundamental role in the clinical manifestations of COVID-19.<sup>10,34–37</sup> During infection, SARS-CoV-2

initiates cell infection by binding to the angiotensin-converting enzyme 2 on the surface of human cells, triggering complex molecular events that lead to high-grade inflammation. Antigen-presenting cells are also infected, leading to the activation, differentiation, and subsequent release of more proinflammatory cytokines.<sup>10,34</sup> The virus's ability to infect T cells causes a decrease in T lymphocytes and an increase in cytokine concentration, thus increasing lymphocytic apoptosis and causing deleterious organic effects and, consequently, greater disease severity.<sup>13,38,39</sup> Qin et al observed that severe cases of COVID-19 have elevated NLRs compared with those of patients with less-severe COVID-19, in which the neutrophil count tends to be higher and the lymphocyte count lower.<sup>40</sup>

Inflammation, nutrition status, and severity in critically ill patients are variables that are widely correlated in the literature; the importance of inflammation and disease severity is well elucidated in the characterization of nutrition risk.<sup>7,9,17,41</sup> Likewise, critically ill patients at high nutrition risk should be identified early, as this condition is directly associated with worse clinical outcomes.<sup>18</sup> When identified as being at high nutrition risk, patients can benefit from nutrition interventions.<sup>42</sup> The systemic inflammation marker NLR can assist in determining this risk because it is associated with the mNUTRIC score,<sup>43</sup> as observed in this study. In agreement with our findings, a previous review and meta-analysis highlighted the NLR as an imperative marker of prognosis for patients with COVID-19. In addition, elevated NLR values on hospital admission are linked to mortality and severity of COVID-19.<sup>44,45</sup>

Although the modified form of the NUTRIC score, which excludes IL-6, has been validated, several studies seek to simplify it by replacing IL-6 with more-available variables, such as CRP.<sup>14,46</sup> The measurement of IL-6 concentrations is not common during the hospital clinical practice, which makes the NUTRIC tool difficult to use in its original form. Likewise, at present, we observed that NLR was related to the mNUTRIC, so it is a promising marker to be studied as a more accessible version to replace the quantification of IL-6. NLR can be calculated in a simple manner by using the white blood cell count, an examination widely available in health services.<sup>35</sup> In this sense, evidence suggests that NLR is a reliable and sensitive marker, as it encompasses the triad immunoinflammatory response, neuroendocrine stress, and disease severity. It can be used to measure stress, intensity of infection, inflammation, and COVID-19 outcomes.<sup>42,43</sup>

There is no consensus on cutoff points for the variables NLR and CRP in patients critically ill with COVID-19. Our sample had a median of 12.6 for NLR and 13.8 mg/dl for CRP. In patients diagnosed with COVID-19, Zeng et al<sup>47</sup> found the sensitivity of NLR  $\geq$  2.6 to predict the worsening of the disease. Moreover, another study also showed that patients with COVID-19 had a median NLR of 2.5 (25th percentile: 1.7; 75th percentile: 3.7),<sup>48</sup> and Song et al observed that critically ill patients had NLR values  $\geq$  5.0.<sup>49</sup> A possible reason why the NLR values are higher than those in the other studies is the mortality rate found in our study—in particular, in the group with high NLRs—because the risk of in-hospital mortality may be 8% higher for every unit increase in NLR.<sup>50</sup>

Although the present study is pioneering for investigating the relationship between the NLR and SGA, NRS, and mNUTRIC, a recent study found an association between NLR values and the prognostic nutrition index in patients with severe COVID-19.<sup>51</sup> Thus, further studies are warranted to investigate NLR levels with other nutrition risk screening and nutrition assessment tools.

## Limitations and strengths

The present study has some limitations: (1) a low number of patients were included in the study; (2) there is a lack of consensus on the cutoff point in the literature on NLR and CRP for this population; (3) the study design does not allow for the establishment of a cause-and-effect relationship; and (4) these tools for assessing nutrition risk should be interpreted with caution because the inherent effect of disease-associated inflammation depends on nutrition adequacy, utilization, and assimilation. As positive points, (1) we emphasize that it is a study that used accessible variables and is easy to apply in clinical hospital practice at low cost, and (2) it is the first study associating the NLR with a nutrition risk tool (mNUTRIC score) in ICU patients with COVID-19, which reinforces the need for further studies in the area.

## CONCLUSIONS

Systemic inflammation caused by COVID-19 may be related to nutrition risk, unfavorable clinical outcomes, and higher mortality in ICU patients. Although the inflammatory marker CRP is the most used in clinical hospital practice, this study showed that NLR was associated with the mNUTRIC score, regardless of sex, age, and BMI. Therefore, it may be interesting to use the systemic inflammatory marker NLR as a complementary tool in the early identification of nutrition risk by performing a more complete nutrition assessment and better prediction of negative clinical outcomes during admission to the ICU in patients with COVID-19.

## ACKNOWLEDGMENTS

Gustavo D. Pimentel would like to The Brazilian National Council for Scientific and Technological Development (CNPq, Brazil, 312252/2019-6).

## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

Paula M. Martins, Emanoelly P. Franco, Liana L. Vieira, Tatyenne L. N. Gomes, and Gustavo D. Pimentel contributed to the study design. Paula M. Martins and Emanoelly P. Franco participated in the collection data. Paula M. Martin and Tatyenne L. N. Gomes performed the bibliographic research and participated in the discussion of the manuscript. Paula M. Martins, Emanoelly P. Franco, Tatyenne L. N. Gomes, Liana L. Vieira, and

Gustavo D. Pimentel wrote the manuscript. All authors participated in the critical discussion of the data, reviewed the manuscript, and read and approved the final version of the article.

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**How to cite this article:** Martins PM, Gomes TLN, Franco EP, Vieira LL, Pimentel GD. High neutrophil-to-lymphocyte ratio at intensive care unit admission is associated with nutrition risk in patients with COVID-19. *J Parenter Enteral Nutr.* 2022;46:1441-1448. <https://doi.org/10.1002/jpen.2318>