Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

The modified NUTRIC score (mNUTRIC) is associated with increased 28-day mortality in critically ill COVID-19 patients: Internal validation of a prediction model

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SUMMARY

Background: High prevalence of malnutrition was found in critically ill COVID-19 patients. The modified Nutrition Risk in the Critically ill (mNUTRIC) score is frequently used for nutritional risk assessment in intensive care unit (ICU) COVID-19 patients. The aim of this study was to investigate the role of mNUTRIC score to predict 28-day mortality in critically ill COVID-19 patients admitted to ICU.

Methods: A cohort of consecutive COVID-19 critically ill patients admitted to ICU was retrospectively evaluated and the nutritional risk was assessed with the use of mNUTRIC score. A multivariable Cox regression model to predict 28-day mortality was therefore developed including the mNUTRIC as a covariate. Internal validation was performed using the bootstrap resampling technique to reduce possible bias in the estimated risks. The performance of the prediction model was assessed via calibration and discrimination.

Results: A total of 98 critically ill COVID-19 patients with a median age of 66 years (56–73 IQR), 81 (82.7%) males were included in this study. A high nutritional risk (mNUTRIC $\geq$5 points) was observed in 41.8% of our critically ill COVID-19 patients while a low nutritional risk (mNUTRIC <5 points) was observed in 58.2%. Forty-five patients (45.9%) died within 28 days after ICU admission. In multivariable model after internal validation, mNUTRIC $\geq$5 (optimism adjusted HR 2.38, 95% CI 1.08–5.25, $p = 0.02$) and high-sensitivity C-reactive protein values (CRP) (optimism adjusted HR 1.02, 95% CI 1.01–1.07, $p = 0.005$) were independent predictors of 28-day mortality.

Conclusions: A high prevalence of malnutrition as revealed by mNUTRIC was found in our critically ill COVID-19 patients once admitted in ICU. After adjustment for covariables, mNUTRIC $\geq$5 and CRP levels were independently associated with 28-day mortality in critically ill COVID-19 patients. The final model revealed good discrimination and calibration. Nutritional risk assessment is essential for the management of critically ill COVID-19 patients as well as for outcome prediction.

1. Introduction

Since the first diagnosis of the Coronavirus Disease 2019 (COVID-19) in China (Wuhan), in December 2019, a pandemic has spread rapidly across the globe. This outbreak has severely affected many countries and their healthcare systems [1]. Several risk factors have been identified to increase the mortality of critically ill COVID-19 patients. Hypertension, diabetes, cardiovascular disease, obesity, older age, higher SOFA score, lymphopenia and high levels of D-dimer, procalcitonin and LDH are associated with a severe form of the disease [2]. Malnutrition represents another independent risk factor for mortality in intensive care unit (ICU) patients [3] while the same findings were also found for COVID-19 critically ill

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patients [4]. As recently underlined by the ESPEN (European Society of Parenteral and Enteral Nutrition) expert statement, the diagnosis and the treatment of malnutrition is one of the principal aims in the management of COVID-19 patients [5]. Moreover, the actual ESPEN guidelines suggest that early nutritional support should be considered in every patient with ICU stay longer than 2 days since a high risk of malnutrition can occur [6].

The Nutrition Risk in the Critically ill (NUTRIC) score, is a suggested screening tool for nutritional assessment of ICU patients [7] and the variable interleukin-6 (IL-6) was excluded in the modified NUTRIC (mNUTRIC) score [8]. Recently, the mNUTRIC score appeared as a promising tool to evaluate the outcome of ICU patients [9] and critically ill COVID-19 patients [10].

The aim of this study was to investigate the role of mNUTRIC score to predict 28-day mortality in critically ill COVID-19 patients admitted to ICU. Moreover, we evaluated the performance of APACHE II, SOFA, and mNUTRIC scoring systems and we verified the optimal mNUTRIC cut-off for outcome prediction.

2. Methods

2.1. Population

This study was approved by the Local Ethics Committee and was conducted at Guglielmo da Saliceto Hospital of Piacenza. We retrospectively analysed a cohort of consecutive critically ill patients admitted to our ICU from March 1, 2020 to May 31, 2020. Critically ill patients were defined as those admitted to ICU who required mechanical ventilation or needed a fraction of inspired oxygen (FiO_2) of at least 60% or more [11]. During the study period, our hospital was quickly changed into a "COVID-19 hospital" to manage a sudden increase in COVID-19 patients requiring hospital admission. Consequently, all the patients admitted to our ICU were COVID-19 patients. COVID-19 infection was diagnosed by a positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs. Pregnant women, children and patients with negative RT-PCR assay were not included in the study.

2.2. Data collection

Electronic medical records were reviewed to collect demographic, clinical and laboratory data. Patients' clinical history including demographic data, medical comorbidities, COVID-19 symptoms duration before hospitalization were also collected. Complete blood cells count, C-reactive protein (CRP), creatinine, glucose, total bilirubin and procalcitonin were considered as laboratory data.

The mNUTRIC score was calculated for each patients within 24 h of ICU admission. This score (0–9 points) was calculated based on five variables: age, acute physiology and chronic health assessment II score (APACHE II), Sequential Organ Failure Assessment (SOFA) score, number of comorbidities and pre-ICU hospital length of stay [10]. The patients were divided in two group based on the mNUTRIC score [10]: high nutritional risk ($\geq$5 points) and low nutritional risk (<5 points).

During the ICU length of stay, every patient received a total energy intake of about 15–20 kcal/kg of actual body weight and the protein intake was 1.2–2 g/kg of actual body weight [12].

2.3. Sample-size calculation

Sample size was calculated based on a previously reported 28-day mortality in critically ill Covid-19 patients equal to 87% and 49% in high and low nutritional risk group respectively [13]. The α (type I error) was set to 0.05 and power = 0.8. The ratio of cases between the low and high nutrition risk groups was set to 1:1. Consequently, a minimum number of 28 patients in the low and 28 patients in the high nutritional risk group were required.

2.4. Statistical analysis

Continuous variables are reported as median and interquartile range while categorical data as relative number and percentage. Mann–Whitney U test, $\chi 2$ test, or Fisher's exact test were used to compare differences between survivors and non-survivors. Risk factors associated with 28 day-mortality were evaluated with a univariable and multivariable Cox proportional hazards regression.

The proportional hazard assumptions were tested and a forward regression analysis was used to select variables accepted in the multivariable model. The Akaike information criterion was used to compare different possible models and determine which one is the best fit for the data.

The internal validation of the model was assessed with non-parametric bootstrap (1000 replications) to obtain random bootstrap samples with replacement from the original database. The prediction model was therefore fitted on each of bootstrap samples. To adjust for optimism, the shrinkage factor (the average calibration slope from each of the bootstrap samples) was applied to the β coefficients of the multivariable model to obtain optimism adjusted hazard ratios for each variable [14].

Model performance was assessed via discrimination and calibration measures. A calibration curve was implemented by plotting predicted against observed probability using adaptive linear spline hazard regression [15].

The TRIPOD (transparent reporting of a multivariable model for individual prognosis or diagnosis) guidance was used to conduct this study and to report the results of the prediction model [16]. Results are expressed as hazard ratio with 95% confidence intervals (95%CI) and p values.

A logistic regression analysis and the area under the receiving operating characteristic (AUC) curve were used to assess the prognostic performance of mNUTRIC, SOFA score and APACHE II.

The Youden index method was used to define the optimal cut-off point of mNUTRIC that maximize the difference between true positive rate and false positive rate for all possible cut-off values [17].

Statistical significance was set at a two tailed P value < 0.05. STATA MP, version 16.0 (STATA Corp., Texas, USA) and R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org) were used for the analyses.

3. Results

98 patients with a confirmed SARS-CoV-2 infection and severe clinical disease expression requiring high-level intensive care treatment were admitted to our ICU during the study period. The median age of the patients was 66 years (56–73 IQR) and 81 patient (82.7%) were male. Almost one comorbidity was present in nearly 61% of patients of which hypertension was the most common (50%), followed by diabetes (19.4%) and heart disease (angina, myocardial infarction or heart failure), 17.3% (Table 1). The most common disease presentation were respiratory symptoms and fever (98% and 91% respectively), followed by gastrointestinal manifestations (vomiting and diarrhea), 16.3%. The median time from respiratory symptoms onset to hospital admission was not different in low nutritional risk group compared to high nutritional risk group (7 days, 6–10 IQR in low mNUTRIC group vs 7 days, IQR 7–10 days in high mNUTRIC group, p = 0.67). The same findings were observed for the length of hospital stay prior to ICU admission (5 days, 1–6

Table 1
Characteristics of the studied population.

Variable	Overall population (n = 98) n. (%)
Age, median (IQR), years	66 (56–73)
Gender	
Male	81 (82.7%)
Female	17 (17.3%)
Comorbidities	
Hypertension	48 (50%)
Diabetes	19 (19.4%)
Cardiovascular disease	17 (17.3%)
Chronic obstructive pulmonary disease	12 (12.2%)
Obesity (BMI ≥30 kg/m2)	9 (9.2%)
Malignancy or history of cancer disease	8 (8.2%)
Chronic kidney disease	4 (4.1%)
Initial symptoms	
Respiratory symptoms	96 (98%)
Fever	89 (91%)
Gastrointestinal symptoms	16 (16.3%)
Cardiovascular symptoms	7 (7.1%)
Time from disease onset to ICU admission, median (IQR), days	12 (9–16)
SOFA score, median (IQR)	4 (3–5)
APACHE II score, median (IQR)	24 (15–26)
Duration of mechanical ventilation, days	9 (5–14)
Treatments in ICU	
CRRT	2 (2%)
Vasopressors	55 (56.1%)
Non-invasive ventilation (C-PAP, bi-level)	3 (3%)
Invasive mechanical ventilation	95 (97%)
Prone positioning	44 (45%)
28-day mortality	45 (46%)

IQR in low mNUTRIC group vs 6 days, 2–9 IQR in high mNUTRIC group, p = 0.28).

A total of 3% of patients received non-invasive ventilation at ICU admission while almost all the patients required invasive mechanical ventilation during the ICU length of stay. A high proportion of patients (56.1%) required vasopressors.

Forty-five patients (45.9%) died in hospital within 28 days after ICU admission and the median time from ICU admission to death was 18 days (IQR 8–43). The characteristics of the studied population is detailed in Table 1.

A high nutritional risk (mNUTRIC ≥5 points) was found in 41.8% of the studied population while a low nutritional risk (mNUTRIC <5 points) was observed in 58.2%. The 28-day mortality was significantly higher in the in the high nutritional risk group than in the low nutritional risk group (80.5% vs 21.1%, p < 0.001) (Fig. 1). Differences between high nutritional risk group and low nutritional risk group are reported in Table 2.

Most of the patients (80%) received enteral nutrition (EN) while 5% received total parenteral nutrition (TPN) and 15% EN + parenteral nutrition (PN). Nasogastric tube was the principal feeding route since only one patient (1.02%) was fed via a nasal jejunal tube. Vomiting and gastric retention occurred in 45% of the patients, while 15% showed diarrhea and 70% hyperglycemia. No differences were found in terms of nutritional support (p = 0.78) and EN intolerance (p = 0.82) in low and high mNUTRIC groups.

Check of the proportionality assumption before regression revealed no violation (p = 0.30). At univariable analysis age (HR 1.03, 95% CI 1.00–1.06, p = 0.03), BMI ≥30 (HR 2.08, 95% CI 1.06–4.10, p = 0.03), white blood cell count (HR 1.08, 95% CI 1.03–1.13, p = 0.002), neutrophils count (HR 1.08, 95% CI 1.03–1.14, p = 0.002), platelets count (HR 0.99, 95% CI 0.99–1.00, p = 0.05), high-sensitivity C-reactive protein value (HR 1.06, 95% CI 1.03–1.09, p < 0.001) and mNUTRIC ≥5 (HR 6.48, 95% CI 3.31–12.69, p < 0.001) were significantly associated with 28-day mortality (Supplementary Table 1).

Based on the multivariable Cox proportional hazards regression analysis, two independent predictors were identified. mNUTRIC ≥5 (HR 2.64, 95% CI 1.20–5.83, p = 0.02) and high-sensitivity C-reactive protein value (HR 1.13, 95% CI 1.12–1.19, p = 0.005) were significantly associated with 28-day mortality (Table 3). In the final internal validated multivariable Cox proportional hazards regression model, mNUTRIC ≥5 (optimism adjusted HR 2.38, 95% CI 1.08–5.25, p = 0.02) and high-sensitivity C-reactive protein value (optimism adjusted HR 1.02, 95% CI 1.01–1.07, p = 0.005) were significantly associated with 28-day mortality (Table 3).

The C-statistic corrected for optimism/overfitting for the prediction of 28-day mortality showed a good discriminatory capacity (C-statistic = 0.72, 95% CI 0.67–0.79). The calibration plot revealed a good calibration of the final model (slope = 0.80, intercept = 0.05) (Fig. 2).

When we compared the performance of different prediction scores for mortality prediction, APACHE-II had a lowest sensitivity of 74% and specificity of 38% (AUC = 0.62, 95%CI: 0.48–0.76), SOFA had 69% and 85% (AUC = 0.80, 95%CI: 0.71–0.84) respectively, whereas mNUTRIC score had the highest sensitivity of 75% and specificity of 89% (AUC = 0.90, 95%CI: 0.84–0.95), Supplementary Fig. 1. The optimal mNUTRIC cut-off associated with the highest Youden index was confirmed as 5 points score.

4. Discussion

The nutritional assessment in critically ill COVID-19 patients is an important element for outcome prediction. In this study patients with high nutritional risk (mNUTRIC ≥5 points) at ICU admission showed an increased probability of 28-day mortality than those with low nutritional risk (mNUTRIC<5 points). Moreover, the mNUTRIC score had the highest sensitivity and specificity for outcome prediction compared to SOFA and APACHEII.

A high prevalence of malnutrition (37.5%) was recently reported in a general cohort of COVID-19 inpatients and 26% of them showed severe malnutrition [18]. The same findings were observed in elderly patients with COVID-19 in a cross sectional study in Wuhan, China [4]. Many possible features can lead to malnutrition in COVID-19 patients. The presence of dyspnea, dysgueusia, anosmia, anorexia, dysphagia, nausea, vomiting and diarrhea can decrease food intake. Simultaneously, caloric and protein intake may be inadequate during the pre-intubation period [5]. Moreover, our patients were kept at home for almost one week before being admitted in the emergency department and this could have influenced the nutritional status.

A state of hyper-metabolism and increased energy expenditure measured by indirect calorimetry were recently observed in a small cohort of critically ill COVID-19 patients [19]. Therefore, acute underfeeding is a possible consequence and it can lead to immunosuppression and to inflammatory response impairment [20]. In fact, almost all our patients showed lymphopenia and even if this finding is common in critically ill COVID-19 patients [21], malnutrition can itself increase lymphopenia and the risk of infectious complications [22].

In ICU the prevalence of malnutrition in COVID-19 patients is even higher (66.7%) [23] and the hypermetabolic phase is prolonged up to 21 days since intubation [24].

The high prevalence of malnutrition in COVID-19 patients and the potential role of individualised nutritional support to improve clinical outcomes and survivals [25] suggest the need to screen the inpatients nutritional risk and to implement individualised nutritional support in patients at risk [26].

The NUTRIC score was developed as a scoring method for quantifying nutrition risk in ICU patients [27] and the American Society for Parenteral and Enteral Nutrition (ASPEN) recommended

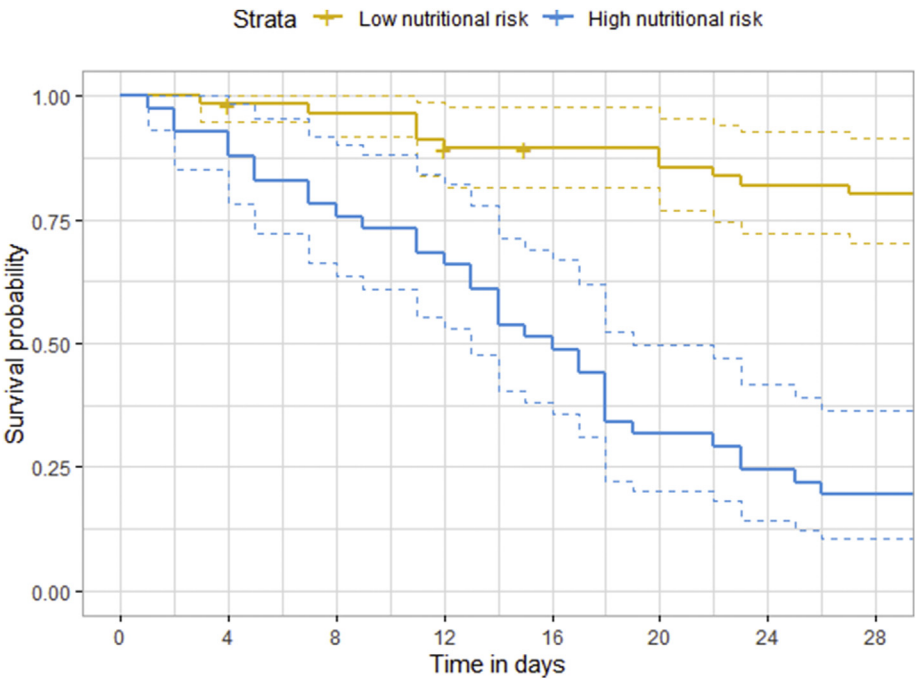

Fig. 1. Survival probability in critically ill COVID-19 patients with high and low nutritional risk. Patients with high nutritional risk (mNUTRIC score ≥5 points) showed a higher 28-day mortality than those with low nutritional risk (mNUTRIC score <5 points), log-rank p < 0.0001.

this score together with the Nutrition Risk Screening 2002 (NRS 2002) for nutritional risk screening in critically ill patients [7]. Conversely, the European Society for Parenteral and Enteral Nutrition (ESPEN) no longer recommended the use of NUTRIC score since is does not include nutritional parameters and it is heavily influenced by APACHE II and SOFA [6]. However, no standardized method currently exists to assess the patient nutritional risk in ICU. The mNUTRIC was the evolution of NUTRIC since IL-6 value was removed from the score because the contribution of this variable was not statistically and clinically useful [27]. Moreover, as it was recently noted, the mNUTRIC and NRS-2002 scores have similar performance in predicting hospital mortality but the mNUTRIC has a better discriminatory ability for mortality prediction in critically ill patients [28]. In our study a high nutritional risk (mNUTRIC ≥5 points) was found in 41.8% of the cohort and the probability for 28-day mortality had more than doubled compared to low nutritional risk (mNUTRIC <5 points) patients. As is was recently reported by Zhang et al., a mNUTRIC score ≥5 was observed in 61% of critically ill COVID-19 patients and the mortality of this group (87%) was significantly higher than in the low nutritional risk group (49%) [13].

Our results are in line with this cited paper and the optimal mNUTRIC cut-off was confirmed as 5 points score for high nutritional risk assessment. On the contrary, almost all our patients required mechanical ventilation and the principal reason for ICU admission was related to the severity of respiratory failure. Since the median time from respiratory symptoms onset to ICU admission was 12 days (9–16 IQR), it is possible to argue that the increased catabolism and the poor nutritional intake worsened the respiratory failure. A global mortality of 46% was found in our critically ill COVID-19 patients and this data is in line with previous findings in our country [29].

Along with the nutritional risk assessment, a recently published meta-analysis showed that higher levels of inflammatory markers such as C-reactive protein (CRP) have been associated with COVID-19 severity and could be considered as prognostic factor [30]. Our predictive model showed that CRP plasmatic levels were independently associated with increased risk of 28-day mortality. In particular, for every increase in one point in CRP levels, the 28-day mortality hazard increased by 2%. It is noteworthy that our results are in keeping with previous studies reporting the role of increased CRP levels in predicting disease severity [31] and the need of mechanical ventilation [32] in COVID-19 patients. Moreover, a positive correlation between CRP concentrations and the extension of lung lesions was also found in COVID-19 patients [33].

Obesity is a frequently reported risk factor for ICU admission and the need of invasive mechanical ventilation [34]. On the contrary, in our multivariable analysis obesity was not a risk factor for mortality in ICU patients. It is important to note that only 9 patients in our cohort showed a BMI ≥30 kg/m^2 in the high and in the low nutritional risk group. Consequently, this variable could have been underpowered. On the other hand, the mortality risk associated with the underweight is frequently reported with an excessively wide confidence interval [35]. However, as we previously found in a large cohort of critically ill COVID-19 patients, only morbid obesity (BMI> 40 kg/m^2) was a risk factors for death [36]. Probably, due to the inability of BMI to differentiate between fat and lean body mass and to account for edema and sodium retention, this variable is less useful for outcome prediction. Moreover, no significant associations was found between body composition and disease severity after bioelectric impedance measurements [37].

The validation of a prognostic model is a fundamental step to implement its use in clinical practice. As it was recently outlined, a possible risk of bias can occur in many prognostication model for patients with COVID-19 due to a lack of validation [38]. Therefore, we decided to use a bootstrap resampling technique for internal validation of our model. The bootstrap resampling draws random samples with replacement from the derivation cohort. Consequently, the prognostic model is evaluated both in the derivation cohort and in the bootstrap sample in order to assess its performance such as discrimination and calibration and to reduce the risk of potential false positive prediction estimates. The mNUTRIC score

Table 2
Differences in clinical characteristics and initial laboratory findings between high and low nutritional risk patients.

Variable	High nutritional risk group (mNUTRIC≥5), n = 41, n (%)	Low nutritional risk group (mNUTRIC<5), n = 57, n (%)	p value
Age, median (IQR), years	60 (53–69)	70 (64–75)	<0.001
Gender			
Male	34 (83%)	47 (82.5%)	0.95
Female	7 (17%)	10 (17.5%)	
Comorbidities			
Hypertension	27 (65.9%)	21 (36.8%)	0.007
Diabetes	13 (31.7%)	6 (10.5%)	0.02
Obesity (BMI ≥30 kg/m^2)	5 (12.2%)	4 (7%)	0.43
Cardiovascular disease	9 (22%)	8 (14%)	0.42
Chronic obstructive pulmonary disease	7 (17.1%)	5 (8.8%)	0.35
Chronic kidney disease	2 (4.9%)	2 (3.5%)	1.00
Malignancy or history of cancer disease	6 (14.6%)	2 (3.5%)	0.07
Initial symptoms			
Fever	38 (92.7%)	51 (89.5%)	0.91
Respiratory symptoms	41 (100%)	55 (96.5%)	1.00
Cardiovascular symptoms	2 (4.9%)	5 (8.8%)	0.69
Gastrointestinal symptoms	7 (17%)	9 (15.8%)	1.00
Hospital LOS before ICU admission, median (IQR), days	5 (2–9)	3 (1–6)	0.08
Vital parameters at ICU admission, median (IQR)			
Heart rate, bpm	88 (70–107)	83 (70–95)	0.33
Respiratory rate, bpm	26 (22–35)	28 (22–33)	0.78
Mean arterial pressure, mmHg	72 (61–90)	81 (67–90)	0.33
Temperature, °C	36.8 (36–37.2)	36.9 (36.5–37.5)	0.09
Laboratory indices at ICU admission, median (IQR)			
White blood cells, x 10^9/L	13.5 (9.2–21.8)	10.1 (6.5–13.4)	0.01
Neutrophils, x 10^9/L	12.5 (8.5–20.1)	8.7 (5.3–12.4)	0.01
Lymphocytes, x 10^9/L	0.48 (0.35–0.69)	0.66 (0.46–0.97)	0.05
Haemoglobin, g/dL	11.8 (10.7–13.2)	12.2 (11–13.4)	0.25
Platelets, x 10^9/L	211 (179–287)	280 (217–340)	0.02
Total bilirubin, mg/dL	1.60 (0.77–2.36)	0.71 (0.64–1.12)	0.001
Urea, mg/dL	71 (50–112)	50 (33–63)	0.001
Creatinine, mg/dL	0.98 (0.79–1.31)	0.75 (0.64–1.17)	0.02
Procalcitonin, ng/mL	0.86 (0.21–1.77)	0.33 (0.11–0.91)	0.04
High-sensitivity C-reactive protein, mg/L	17.25 (9.3–23.6)	10.20 (3.69–16.87)	0.04
Glucose, mg/dL	169 (124–201)	130 (120–151)	0.14
GCS score, median (IQR)	13 (4–14)	15 (14–15)	0.003
SOFA score, median (IQR)	6 (4–7)	3 (2–4)	<0.001
APACHE II score, median (IQR)	27 (24–29)	15 (12–24)	<0.001
Duration of mechanical ventilation, median (IQR), days	9 (5–17)	8.5 (5–11)	0.44
Treatments in ICU			
CRRT	1 (2.4%)	1 (1.8%)	1.00
Vasopressors	27 (65.9%)	28 (49.1%)	0.035
Non-invasive ventilation (C-PAP, bi-level)	0	3 (5.3%)	0.15
Invasive mechanical ventilation	41 (100%)	54 (94.7%)	0.38
Prone positioning	20 (48.8%)	24 (42.1%)	0.49
28-day mortality	33 (80.5%)	12 (21.1%)	<0.001

Table 3
Multivariable Cox proportional hazards regression analysis of factors associated with mortality.

Variable	HR	95% CI	p value	Optimism adjusted HR	Optimism adjusted 95% CI
mNUTRIC ≥ 5	2.64	1.20–5.83	0.02	2.38	1.08–5.25
High-sensitivity C-reactive protein, mg/L	1.13	1.12–1.19	0.005	1.02	1.02–1.07
Neutrophils, x 10^9/L	1.05	0.99–1.11	0.12	0.95	0.90–1.00

was recently confirmed as a useful tool to predict mortality of ICU COVID-19 patients [13,39–44]. On the contrary, Liberti et al., reported a low discriminative ability of NUTRIC and mNUTRIC scores to predict ICU mortality of COVID-19 patients [45]. Some possible reasons for these different results can be found in the limited number of patients included and no covariates adjustment along with very short interval between hospital and ICU admission compared to other studies.

To our knowledge, our study is the first internal validated model with the use of mNUTRIC score to predict 28-day mortality in critically ill COVID-19 patients. Moreover, the use of mNUTRIC improved the outcome prediction ability compared to our previously published study [46]. However, even if our model showed a good discriminatory accuracy for 28-day mortality prediction in critically ill COVID-19 patients, more prospective studies are needed to evaluate the role of mNUTRIC and how to reduce malnutrition onset in these patients.

This study has several limitations. First, it is a single centre retrospective study during a pandemic that heavily affect medical resources. Therefore, some data might present inaccuracies and bias.

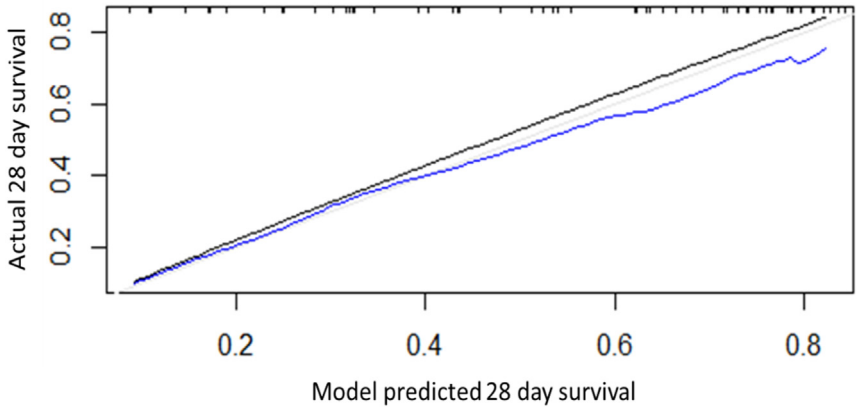

Fig. 2. Bootstrap estimate of calibration accuracy for 28-day mortality estimates from the final Cox model, using adaptive linear spline hazard regression. The line nearer the ideal line corresponds to apparent predictive accuracy. The blue curve corresponds to bootstrap-corrected estimates.

A limited number of subjects were enrolled, however this issue is quite counteracted by the internal validation process. Nutritional risk assessment was performed at ICU admission and no dynamic evaluations were provided. Consequently, we cannot infer the role of nutritional support in terms of outcome and if the nutritional risk changed over time. We did not use the NRS-2002 score to evaluate nutritional status since it was not specifically developed for ICU patients. Moreover, as it was recently reported by Achean et al., mNUTRIC score was able to with higher prognostic accuracy compared to NRS-2002 for early mortality prediction in ICU patients affected by severe pneumonia [41]. Another major problem is the lack of albumin and pre-albumin levels or others rapid-turnover visceral proteins or muscle mass assessment in our patients as classical laboratory indexes for nutritional assessment [47,48]. These data were available in only a small amount of patients without reaching the required minimum sample size to be analysed. However, albumin and pre-albumin levels are mainly indicators of the inflammatory status and probably they are poor reliable nutritional indexes in presence of inflammatory state induced by SARS-CoV-2. Another major limit of our study is the lack of body composition parameters such as skeletal muscle index, visceral adiposity and sarcopenic obesity with a possible high predictive value for mortality in ICU patients. The principal aim of our study was to simply investigate the role of different clinical risk scores (mNUTRIC, SOFA and APACHE II) to predict 28-day mortality in critically ill COVID-19 patients admitted to ICU and at the time of writing this paper all the patients concluded the follow-up period.

Further analyses are certainly needed to confirm these results and to evaluate the role of mNUTRIC to predict complications such as secondary infection, organ failure or thrombosis during the ICU length of stay of critically ill COVID-19 patients.

5. Conclusions

A high nutritional risk (mNUTRIC $\geq$5 points) was found in 41.8% of critically ill COVID-19 patients admitted to ICU and this data correlate with higher negative outcome prediction and observed deaths. In our internal validated multivariable model mNUTRIC $\geq$5 along with CRP values were independent predictors of 28-day mortality. When compared to other prediction score for mortality (SOFA and APACHE-II), high mNUTRIC showed the highest sensitivity and specificity for 28-day mortality of critically ill COVID-19 patients admitted to ICU. Nutritional risk assessment is essential in critically ill COVID-19 patients to provide appropriate nutrition support.

Future studies with increased patients number and longer follow-up are needed to confirm our findings.

Ethics approval and consent to participate

This study was approved by the Ethical Committees of Area Vasta Emilia Nord; protocol: 1066/2020/OSS*/AUSLPC; date of approval: (October 20, 2020).

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contribution

MLGL, EM and MB collected the epidemiological and clinical data. LMLG performed the statistical analysis and drafted the manuscript. NM and MZ revised the final manuscript and contributed substantially to the study design.

Declaration of competing interest

The authors certify that they have no affiliation with, or involvement in any organization or entity with any financial or non-financial interest in the subject matter discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.02.014.

Abbreviations

mNUTRIC	modified Nutrition Risk in the Critically ill score
COVID-19	Coronavirus Disease 2019
ICU	intensive care unit
APACHE II	Acute Physiology and Chronic Health Disease Classification System II
SOFA	Sequential Organ Failure Assessment
GCS	Glasgow Coma Scale
CRP	C-reactive protein
AUC	receiving operating characteristic
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
EN	enteral nutrition
TPN	total parenteral nutrition
PN	parenteral nutrition
IQR	Interquartile Range
BMI	body mass index
HR	hazard ratio
LOS	Length of Stay
C-PAP	continuous positive airway pressure
CRRT	continuous renal replacement therapy

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