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 validity of the global leadership initiative on malnutrition criteria for diagnosing malnutrition in critically ill patients with COVID-19: A prospective cohort study

Shaahin Shahbazi [a], Melika Hajimohammadebrahim-Ketabforoush [b], Maryam Vahdat Shariatpanahi [d], Erfan Shahbazi [c], Zahra Vahdat Shariatpanahi [b, *]

[a] Department of Gastroenterology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, Iran
[b] Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Food science, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[d] Department of Psychiatry, Faculty of Medicine, Islamic Azad University of Medical Sciences, Tehran, Iran

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SUMMARY

Background and aim: We conducted the present study to investigate the nutritional status of critically ill COVID-19 patients and validate the GLIM criteria with respect to the SGA.
Methods: In this prospective cohort study, 109 ICU patients were assessed for malnutrition based on GLIM and SGA criteria. The relation between nutrition assessment tools and duration of hospitalization and mortality were also evaluated. The sensitivity and specificity of GLIM criteria concerning the detection of malnutrition was assessed based on the area under the curve.
Results: Malnutrition, according to the SGA and GLIM criteria, was found in 68 (62.4%) and 66 (61.5%) of our subjects. There was an optimal agreement between the GLIM criteria and the SGA criteria regarding malnutrition diagnosis ($K = 0.85$, $P < 0.001$). The area under curve for the GLIM was stratified based on the SGA results and was 0.927 (95% CI: 0.868–0.985) with a sensitivity and specificity of 92% and 93%, respectively.
Conclusion: Malnutrition is frequently observed in critically ill COVID-19 patients. GLIM criteria is a valid tool and has a strong association with mortality and longer duration of ICU stay.

1. Introduction

Malnutrition is known as an underlying risk factor for both more severe affliction and worse outcomes due to various respiratory infections [1–4]. Moreover, in COVID-19 patients, a growing body of evidence have discussed that malnutrition could be a poor prognostic factor for morbidity and mortality [5,6]. COVID-19-related malnutrition could be manifested as a result of hyperinflammation state, anorexia, and consequently, decreased food intake and assimilation, hyper-metabolism, comorbidities, elderly, and prolonged hospitalization [7–9]. The prevalence of malnutrition in these patients has been reported to range from 42% to 66.7% in different studies [9–11]. This rate is higher in critically ill cases [9]. In these previous studies, malnutrition has been screened and diagnosed employing various tools, such as the modified NRS-2002 tool suggested by ESPEN for screening [8], the nutritional risk index (NRI) for defining nutritional risk [5], the mini nutritional assessment (MNA) for assessing either nutritional risk or malnutrition [11], and the global leadership initiative on malnutrition (GLIM) criteria for the diagnosis of malnutrition [8,9]. GLIM criteria is a novel diagnostic tool for malnutrition proposed in 2018 by the global clinical nutrition community [12]. It comprises two parts, including phenotypic criterion (non-volitional weight loss, low

* Corresponding author. 3, Baran, West Arghavan, Farahzadi Blvd., Shahrak Qods, PO Box: 19395-4741, 1981619573, Tehran, Iran. Fax: +98(21) 22376467.
E-mail addresses: mdkabe@gmail.com (S. Shahbazi), ketabforoshm@gmail.com (M. Hajimohammadebrahim-Ketabforoush), drmvahdat@yahoo.com (M. Vahdat Shariatpanahi), ershfst@gmail.com (E. Shahbazi), nutritiondata@yahoo.com (Z. Vahdat Shariatpanahi).

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BMI) and etiologic criterion (reduced food intake or assimilation, disease burden/inflammatory condition) [12]. Given the importance of early diagnosis of malnutrition, the rapid onset of nutritional support, and its potential impact on disease prognosis in COVID-19 patients, European Society of parenteral and enteral nutrition (ESPEN) has recently released expert statements and practical guidance in which it recommended the use of GLIM criteria for diagnosing malnutrition in COVID-19 patients [13]. However, Subjective Global Assessment (SGA) is often used as a diagnostic tool for malnutrition [14]. There is a great deal of evidence to support GLIM criteria [15,16] while certain studies have considered it as a malnutrition diagnostic tool with fair sensitivity and specificity in clinical settings compared with SGA [17]. Even though few recent studies on COVID-19 patients have examined malnutrition via GLIM criteria [8,9], no studies in this regard have examined the validity of this malnutrition diagnostic tool. All critically ill COVID-19 patients have severe inflammation; accordingly, they have one etiologic criterion of GLIM. Hence, at least one phenotypic criterion should be present for diagnosis of malnutrition. This saves the time, accelerates the assessment, and reduces the contact time with infected patients. Therefore, in the present study, we evaluated the validity of GLIM criteria for malnutrition in critically ill COVID-19 patients with respect to the SGA. Furthermore, we investigated the relation between nutrition assessment tools and clinical outcomes.

2. Materials and methods

2.1. Study design and participants

This prospective cohort study was conducted in a university hospital on critical COVID-19 patients from June 2020 to January 2021. The study protocol was approved by the responsible ethics committee, and the informed consents were obtained from all the patients or their legal representative prior to their enrollment. Herein, we included the patients over the age of 18 with positive real-time fluorescence polymerase chain reaction (RT-PCR) for COVID-19 initiating nutritional support within 72 h following the hospital admission. The exclusion criteria included pregnancy, participation in interventional trials, and patients without weight and height data. Disease severity was classified based on guidelines of National Health Commission of the People's Republic of China [18]. According to that, critically ill patients were defined as cases with respiratory failure, shock, or multiorgan dysfunction, who should be treated in intensive care unit (ICU).

2.2. Data collection

During the first 48 h of ICU admission, before the potential development of edema, anthropometric measurements were obtained and nutritional assessment was carried out utilizing both SGA and GLIM assessment tools. To diagnose malnutrition by applying the GLIM criteria, at least one phenotype and one etiologic criterion should be present. The phenotype criteria included non-volitional weight loss >5% within the past 6 months, or >10% beyond 6 months, low BMI (kg/m^2): <18.5 if <70 yr, or <20 if >70 yr (based on definition for Asian), and reduced muscle mass. Etiologic criteria included reduced food intake ($\leq$50% of energy requirement > 1 week, or any reduction for >2 weeks or any chronic malabsorption), and disease burden/inflammation [16]. In our study, since the patients were suffering from a critical condition, all of them met the disease burden and inflammation criterion and therefore, all had one of the etiologic criteria of GLIM assessment. It was not possible to measure weight and height in most patients and we were satisfied with self-report by the patients or their caregivers. BMI was calculated as weight in kilograms divided by height in meters squared. Owing to safety and hygiene reasons, muscle mass status was evaluated measuring mid arm muscle circumference (MAMC). The MAMC was calculated using the MAMC = MAC − ($\pi \times$ TSF) formula. Mid arm circumference (MAC) was measured using non-stretch tape, at the halfway point between the olecranon process of the ulna and the acromion process of the scapula; the average of the two measurements was recorded. Triceps skinfold thickness (TSF) was measured at the same point. A value lower than fifth percentile based on age and gender was considered for reduced muscle mass.

To perform SGA, the patients or their care givers answered questions about nutrient intake in the past two weeks, weight loss, eating habits, and gastrointestinal symptoms (if possible); the stress imposed by the disease was also recorded. In addition, we performed physical examination for all the subjects in order to find the loss of subcutaneous fat (orbital, triceps and the mid-axillary line at the level of the lower ribs) and muscle waste (temple, clavicle, shoulder, scapula, quadriceps, and back of hand areas). Categorization of SGA is as follows: well nourished (A), moderately malnourished (B), and severely malnourished (C) [19]. In our study, the patients with SGA class B and C were considered malnourished for the analysis.

2.3. Outcomes

The duration of ICU stay, and in-ICU death were recorded and considered as the main outcomes.

2.4. Statistical analysis

SPSS software (Statistical Package for the Social Sciences version 20; Chicago, IL, USA) was used for data analysis. The statistical significance was determined at $P < 0.05$. The Kolmogorov–Smirnov test was utilized to check the normality of the distribution of variables. Descriptive statistics were used to characterize and summarize the participant characteristics. Continuous variables were repoMNA

rted as mean ± standard deviation (SD), or median (interquartile range [IQR]), and compared with the Student *t*-test or Mann–Whitney U-test, respectively. Categorical variables were presented as frequencies and percentages. Chi-square ($\chi 2$) test was performed to check the differences in the distribution of categorical variables. In order to evaluate the diagnostic concordance between the GLIM and the SGA, we performed Cohen's kappa statistic (K). According to the K value, $K \leq 0$ was defined as no agreement, 0.01–0.20 as poor, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as optimal agreement. In order to evaluate the sensitivity and specificity of GLIM in diagnosis of malnutrition stratified by the SGA results, receiver-operating curves (ROC curve) analysis was performed. The ROC analysis results were interpreted as follows: AUC < 0.70 represented low diagnostic accuracy, area under curve (AUC) in the range of 0.70–0.90 showed moderate diagnostic accuracy, and AUC $\geq$ 0.90 depicted high diagnostic accuracy.

Logistic regression analysis was used to assess the relationship between malnutrition and clinical outcomes (mortality, duration of hospitalization). In this model duration of hospitalization in the ICU was categorized by its median to two groups. Any covariates associated with the response variables in univariate analysis, retained in the final model or multivariate logistic regression.

3. Results

A total of 109 patients met the study eligibility criteria, including 51 (47%) females and 58 (53%) males (Fig. 1). Table 1 represents demographic and clinical characteristics of these patients. The mean age was 60.90 ± 13.7 years. The median days from illness onset to

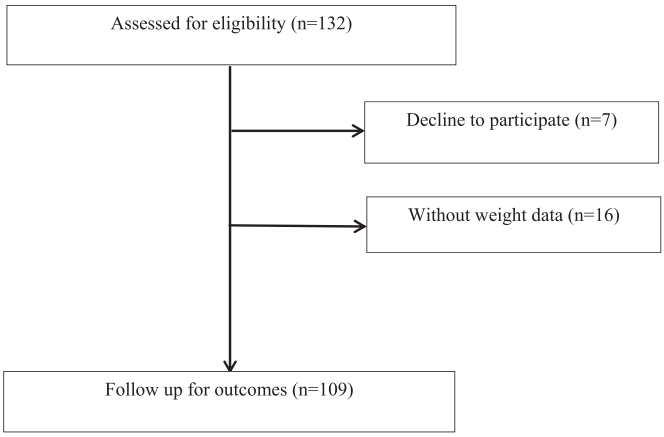

Fig. 1. Study flowchart.

admission was 8 [7,8]. The mean APACHE score was 14.87 ± 3.87, which was obtained in the first 24 h of admission in ICU. Comorbidity was present in 42 (38.5%) of the patients. Chronic obstructive pulmonary disease, Hypertension and cardiovascular disease, and type 2 diabetes was observed in 15, 13, and 14 patients, respectively.

Malnutrition according to the SGA and GLIM criteria was found in 68 (62.4%) and 66 (61.5%) patients.

As shown in Table 2, among phenotypic criteria in the GLIM, weight loss had the highest prevalence, followed by muscle loss and low BMI. According to SGA, after gastrointestinal symptoms, weight loss had the highest frequency, followed by muscle and fat mass loss. Reduced food intake was reported prior to hospitalization in 88 (83%) patients.

There was an optimal agreement between the GLIM criteria and the SGA criteria in the diagnosis of malnutrition (K = 0.85, P < 0.001).

The AUC for the GLIM was 0.927 (95% CI: 0.868–0.985) with a sensitivity and specificity of 92% and 93%, respectively (Fig. 2).

To determine the relation between malnutrition and outcomes, logistic regression analysis was performed (Table 3). Malnutrition based on GLIM was associated with longer duration of hospitalization (≥15 days) (OR: 3.43; 95% CI, 1.16–10.15; P = 0.02), and higher in ICU mortality (OR: 4.83; 95% CI, 2.09–11.15; P < 0.001). Similarly, being malnourished according to SGA was associated with longer hospitalization (≥15 days) (OR: 5.21; 95% CI, 1.68–16.17; P = 0.004), and higher in ICU mortality (OR: 6.06; 95% CI, 2.53–14.50; P < 0.001). As age and comorbidity were associated with mortality, multivariate logistic regression analysis was employed to determine the relation between malnutrition and mortality while controlling age and comorbidity (OR: 4.01; 95% CI, 1.44–11.2; P = 0.008 for GLIM and OR: 6.07; 95% CI, 1.90–19.40; P = 0.002 for SGA).

4. Discussion

According to the obtained results, GLIM had an optimal agreement with the SGA and a high validity in detecting malnutrition in critically ill COVID-19 patients. Additionally, the prevalence of malnutrition was high in critically ill COVID-19 patients at the time of admission (SGA: 62.4%; GLIM: 61.5%). Furthermore, the risk of longer ICU stay was 4.5 folds higher in the malnourished cases based on GLIM criteria and 5 folds higher based on SGA. The risk of mortality was also independently 3 folds higher in the malnourished cases according to GLIM criteria and 5 folds according to SGA.

Malnutrition is believed to be highly frequent in COVID-19 infection and the critically ill patients are involved the most [20]. It is because most of them spent a period of their disease as mild, moderate, or severe forms before the disease got critical. Accordingly, the majority of patients experience low calorie intake and weight loss, before admitting to ICU.

In fact, there is a vicious cycle between malnutrition and inflammation of the disease. Inflammation leads to anorexia and decreased calorie intake on top of increased energy requirements; therefore, malnutrition intensifies the inflammation. This necessitates the diagnosis of malnutrition in COVID-19 patients and should be assessed as soon as possible at the time of admission.

Table 1
Characteristics of COVID-19 patients based on GLIM and SGA.

Variable	GLIM			SGA		
	Mal-nourished N = 66	Well-nourished N = 43	P value	Mal-nourished N = 68	Well-nourished N = 41	P value
Age	67.37 ± 11.80	51.13 ± 10.39	<0.001	66.34 ± 11.37	51.24 ± 8.28	<0.001
Female, n (%)	34 (52)	17(40)	0.22	35 (52)	16 (39)	0.20
Days from illness onset to admission	8 (7–9)	8 (7–9)	0.25	8 (7–9)	8 (7–9)	0.70
APACHE II	14.48 ± 3.53	15.10 ± 4.05	0.27	14.43 ± 2.72	15.11 ± 2.94	0.23
Serum albumin (g/dL)	2.92 ± 0.2	3.01 ± 0.2	0.51	2.91 ± 0.2	3.03 ± 0.2	0.52
O_2 therapy						
HFNC	14 (21)	7 (16)		16 (24)	5 (12)	
NIV	23(35)	12 (28)		22 (32)	13(32)	
MV	29(44)	24 (56)	0.47	30 (44)	23 (56)	0.29
Mean ICU energy intake	1445.10 ± 211.98	1385.18 ± 200.61	0.14	1426.60 ± 206	1413.8 ± 215.25	0.76
Energy intake ratio (%)[a]	81.21 ± 19.37	82.55 ± 18.79	0.51	81.90 ± 17.44	82.30 ± 19.09	0.62
Comorbidity, n (%)	30 (46)	12 (28)	0.06	32 (47)	10 (24)	0.01
Diabetes	10	4		11	3	
Cardiovascular	10	3		10	3	
Hypertension	10	5		11	4	
Medication, n (%)						
Antiviral	(100)	(100)	1	(100)	(100)	1
Antibiotic	47 (71)	6 (14)	<0.001	50 (74)	3 (7)	<0.001
Glucocorticoid	(100)	(100)	1	(100)	(100)	1
Days of ICU stay	21.60 ± 4.59	17.23 ± 3.83	<0.001	22.01 ± 4.46	16.34 ± 4.87	<0.001
Mortality, n(%)	43 (65)	12 (28)	<0.001	45 (66)	10 (24)	<0.001

GLIM, global leadership initiative on malnutrition; SGA, subjective global assessment; APACHE, acute physiology and chronic health evaluation; HFNC, high flow nasal cannula; NIV, non-invasive ventilation; MV, mechanical ventilation; ICU, intensive care unit.

[a] Mean actual energy intake divided by target intake.

Table 2
Number of positive items of SGA and GLIM in patients.

	Reduced food intake[a]	Disease burden/inflammation[a]	Symptoms Anorexia/weakness[a]	Weight loss[a]	Low BMI[a]	Low muscle mass[a]	Loss of fat[a]
SGA	88	109	93	48	–	49	31
GLIM	88	109	93	48	7	27	–

SGA, subjective global assessment; GLIM, global leadership initiative on malnutrition; BMI, body mass index.
[a] Number of patients.

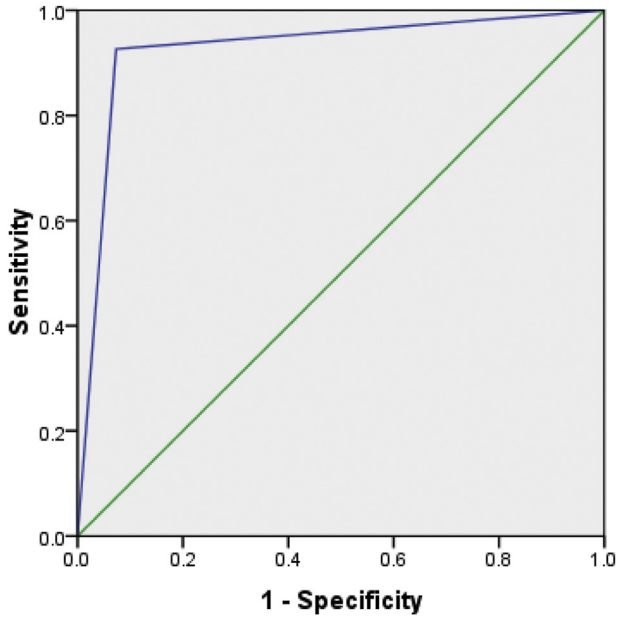

Fig. 2. Receiver operating characteristic (ROC) curve for prediction of malnutrition using GLIM. The area under the curve is: 0.927 (95% CI: 0.868–0.985).

GLIM is a new nutritional assessment tool proposed by the global clinical nutrition community in 2018 [12]. A study conducted on non-COVID critically ill patients evaluated the validity of GLIM criteria concerning the diagnosis of malnutrition in comparison with the SGA. It reported that the AUC, for GLIM criteria, was 0.85 ($P < 0.001$) with a sensitivity and specificity of 85% and 79%, respectively. The association with clinical outcomes was not evaluated in that study [21].

Another study conducted on post ICU COVID-19 patients reported that the prevalence of malnutrition according to GLIM criteria was 66.7%. Therein, no relationships were observed between malnutrition and clinical outcomes, including transfer to ICU and death [9].

Another study conducted on hospitalized COVID-19 patients reported that the prevalence of malnutrition according to GLIM criteria was 70% in critically ill patients. Its clinical outcomes were not assessed in this study [20].

Certain studies have suggested performing early Nutrition Risk Score (NRS) for COVID-19 patients in order to screen malnutrition [22]. As APACHE score of these patients is usually over 10, based on NRS scoring system, most patients are at nutrition risk. On the other hand, ESPEN 2018 guidelines in ICU recommend that staying in ICU longer than 48 h should be considered at the investigation of malnutrition-associated risks [23]. Thus, it seems that the assessment of nutrition via SGA or GLIM should be performed as soon as possible at the time of admission and perhaps with no need for nutrition screening before the assessment in critically ill COVID-19 patients.

In our study, since the patients were suffering from a critical condition, all of them met the disease burden and inflammation criterion and therefore, all had one of the etiologic criteria of GLIM assessment. Therefore, anyone with low BMI, weight loss, or reduced muscle mass, was considered as malnourished. This was also true for the SGA, as the item of stress imposed by the disease was considered positive in all the patients. Some items of SGA in critically ill patients are often inapplicable, such as the item of functional capacity, specifically in patients who receive sedatives. This is also true for the item of edema usually present in critically ill ones, which is related to inflammation and increased vascular permeability. There are similarities in other items of SGA and GLIM, including reduced nutrient intake, weight loss, and disease burden/inflammation. Reduced food intake with a strong validity is a well-established etiologic criterion for malnutrition in both SGA and GLIM. Experiencing the symptoms affecting oral intake, which is an item of SGA, including poor oral health, anorexia, and gastrointestinal complaints like dysphagia, nausea, vomiting, diarrhea, constipation, and abdominal pain, are also incorporated in GLIM criteria as supportive indicators to help identifying poor food intake or absorption. The above-mentioned findings confirmed the similarity of GLIM to SGA about detecting malnutrition in critically ill patients. The item of muscle mass loss, which is incorporated in both SGA and GLIM, has a difference concerning the method of measurement. GLIM recommends dual-energy absorptiometry, sonography, bioelectrical impedance analysis, computed tomography, or magnetic resonance imaging for muscle size measurement; meanwhile, as they are often not available, the measurement of calf or arm muscle circumference is considered as alternative measures [23]. There are few reference data available for circumferences of the arm and calf in different races and thus, GLIM working group has stated that additional research is warranted to establish general reference standards for some specific populations, such as Asians. Furthermore, the calculation of muscle area of the arm would not be accurate or valid in the obese [24]. By performing SGA, loss of muscle mass is assessed by observing temple, clavicle, shoulder, scapula, and quadriceps muscles, which is a rapid assessment and also identical in different sex and races. Moreover, since there is less contact with the patient, there is more prevention of infection. Hence, in COVID-19 patients it might be better to measure muscle mass based on SGA definition.

In the current study, for the first time, we evaluated the validity of GLIM concerning the diagnosis of malnutrition in ICU hospitalized COVID-19 patients. It was a prospective cohort study and evaluated the association of malnutrition with the duration of hospitalization and mortality in ICU considering the cofounding variables.

However, our study had certain limitations. Primarily, it was a single-center study. Secondly, in order to prevent contamination, MAMC was measured by a nurse who was trained to apply the method of measurement and was recovered from COVID-19 infection while being supervised by the researcher. In addition, MAMC measurement is difficult in those with obesity and edema. Normative values used for MAMC measurement was not population-specific. Moreover, height and weight data were

Table 3
Bivariate logic regression of GLIM and SGA associated with outcomes.

Mortality						
Variable	OR	CI	P value	Adjusted OR[a]	CI	P value
Malnutrition						
GLIM	4.83	2.09–11.15	<0.001	4.01	1.44–11.12	0.008
SGA	6.06	2.53–14.50	<0.001	6.07	1.90–19.40	0.002
Comorbidity	2.96	1.32–6.63	0.008			
Age	1.04	1.01–1.07	0.005			
Duration of IU stay						
Malnutrition						
GLIM	3.43	1.16–10.15	0.02			
SGA	5.21	1.68–16.17	0.004			

GLIM, global leadership initiative on malnutrition; SGA, subjective global assessment; ICU, intensive care unit.
[a] Adjusted by comorbidity and age.

self-reported by the patients or caregivers, which might not be accurate. Another limitation of ours was the subjective nature by definition of SGA. Our work would be much more accurate if we measured other more related outcomes to nutritional status, such as in post discharge follow-up.

5. Conclusion

The prevalence of malnutrition is high at the time of admission in critically ill COVID-19 patients. GLIM is a valid tool for the diagnosis of malnutrition in this group of patients. Since all critically ill COVID-19 patients have one of the etiologic criteria of GLIM assessment, the presence of one phenotypic criterion confirms the malnutrition. Hence, GLIM accelerates the assessment and reduces the duration of vicinity with the infected patient in comparison to SGA. GLIM and SGA are both strongly associated with in-hospital mortality and length of stay in the ICU.

Ethics approval and consent to participate

This prospective cohort study was performed in accordance with the guidelines of the Declaration of Helsinki. In the beginning of the study, informed consent was obtained from patients. The study was approved by the Ilam University of Medical Sciences ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study adheres to STORBE guidelines.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by S.S, Z.V, M.H.K, M.V and E.S. The first draft of the manuscript was written by Z.V and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare that they have no competing interests.

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Abbreviations

AUC	area under curve
BMI	body mass index
ESPEN	European Society of parenteral and enteral nutrition
GLIM	global leadership initiative on malnutrition
ICU	intensive care unit
ROC curve	receiver operating characteristic curve
RT-PCR	real-time fluorescence polymerase chain reaction
SGA	subjective global assessment

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