International Journal of General Medicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Comparative Study of Different Inflammation Definition Methods of GLIM in the Diagnosis of Malnutrition in Patients with Acute Pancreatitis

Hao Fu[1], Ping Li[2], Jie Yang[1], Hui Jiang[1]

[1]Nutrition Department, Affiliated Hospital of Chengde Medical University, Chengde, People's Republic of China; [2]Gastroenterology, Affiliated Hospital of Chengde Medical University, Chengde, People's Republic of China

Correspondence: Hao Fu, Nutrition Department, Affiliated Hospital of Chengde Medical University, No. 36, Nanyingzi Street, Chengde, Heibei, 067000, People's Republic of China, Tel +86 0314 2279680, Email williamfu85@163.com

Purpose: This study aims to investigate the influence of the Global Leadership Initiative on Malnutrition (GLIM) on diagnosing malnutrition in acute pancreatitis (AP) based on various inflammatory criteria.

Patients and Methods: A total of 258 AP patients admitted to a large medical center between June 2019 and January 2022 were retrospectively analyzed. All patients underwent evaluation using the original GLIM and GLIM criteria based on C-reactive protein (CRP), albumin, neutrophil/lymphocyte ratio, and CRP/albumin ratio (CAR). The study explored the impact of malnutrition diagnosis using different GLIM criteria on various clinical outcomes of AP patients and assessed the agreement of different GLIM criteria compared to the original GLIM.

Results: Thirty-seven (14.34%) patients were malnourished according to the original GLIM criteria. Using the other four criteria, malnutrition rates ranged from 6.59% to 12.40%. Malnutrition diagnosed by all GLIM criteria was associated with local complications. Malnutrition identified by the original, CRP-based, and CAR-based GLIM criteria was also associated with infectious complications and composite outcomes. Meanwhile, albumin-based malnutrition was associated with all adverse outcomes except organ failure. When considering all four GLIM criteria except the original one, malnourished patients exhibited longer lengths of stay than non-malnourished patients. Under the CRP- and albumin-based GLIM criteria, hospitalization costs were higher for malnourished patients. The sensitivity analyses demonstrated the robustness of the results. The agreement of the four GLIM criteria with the original GLIM criteria were consistent with the corresponding incidence of malnutrition.

Conclusion: This study validated the GLIM criteria for the first time in AP. Malnourished patients were more likely to experience local complications than non-malnourished AP patients. However, the inconsistency between GLIM criteria based on disease burden and various inflammatory markers was significant. The inflammatory marker-based GLIM criteria demonstrated a stronger predictive value than the original GLIM criteria in assessing prognosis in AP patients.

Keywords: acute pancreatitis, GLIM criteria, inflammatory marker, malnutrition, outcome

Introduction

Acute pancreatitis (AP) is one of the most common acute diseases of the gastrointestinal tract. The 2012 revision of the Atlanta Classification categorizes AP as mild, moderately severe, or severe.[1] In AP, especially in moderately severe AP and severe AP (SAP), inflammatory and septic complications increase metabolism, energy requirements, and proteolytic metabolism. Additionally, AP patients tend to eat less due to abdominal pain. Hence, all AP patients are at risk of malnutrition.[2] Malnutrition and the risk of malnutrition are associated with adverse outcomes, including higher complication rates, prolonged length of stay (LOS) and increased mortality.[3–5] Therefore, assessing the nutritional status of AP patients is crucial. However, the diagnostic criteria for malnutrition vary, leading to inconsistencies in comparisons among studies.

Received: 3 July 2024
Accepted: 22 October 2024
Published: 24 October 2024

To standardize the current diagnostic criteria for malnutrition in hospitalized adults, the Global Leadership Initiative on Malnutrition (GLIM) working group published new diagnostic criteria for malnutrition in 2018, including phenotypic and etiologic criteria.[6] One of the etiologic criteria for GLIM is inflammation; however, the original GLIM construct description provided limited guidance on how to assess inflammation to support the diagnosis of malnutrition. This lack of clarity has resulted in inconsistencies in the methods used to determine inflammation in studies validating the GLIM criteria. For instance, a review of GLIM studies involving older adults revealed a variety of approaches used to assess inflammation: more than half relied solely on the diagnosis of inflammatory disease, while others primarily used C-reactive protein (CRP) alone or in combination with the presence of inflammatory disease.[7] To tackle the issue of inflammation assessment in the GLIM criteria, the GLIM working group published a guidance in late 2023 suggesting that the presence of acute or chronic disease, infection, or injury typically associated with inflammatory activity may satisfy the GLIM disease burden/inflammation criteria, ie, confirmation by laboratory markers was not always necessary, and the guidance enumerated diseases that include AP.[8] The guidance recommended that laboratory markers be measured in uncertain cases to help confirm the inflammatory character of the underlying disease or condition. The use of CRP ≥3 mg/L was recommended and a dozen different types of alternative laboratories have also been mentioned, including albumin, CRP/albumin ratio (CAR), and neutrophil/lymphocyte count ratio (NLR). Albumin is a negative acute phase reactant and low serum albumin levels indicate severe inflammation.[9] In recent years, clinicians have increasingly considered CAR as a new inflammatory marker (IM). A study showed that CAR was significantly associated with SAP and the area under the curve for the receiver operating characteristic curve was 0.68, higher than Ranson's criterion (0.62) for SAP. The optimal cutoff value for predicting SAP was 7.51, with a sensitivity of 63.4% and a specificity of 65.6%.[10] NLR is also associated with the prognosis in AP. Azab et al found that a high NLR was a significant predictor of intensive care unit (ICU) admissions and prolonged LOS in AP. They suggested using an NLR cutoff of >4.7 as a simple indicator of severity in AP.[11] The findings of Jeon et al were very similar, with the optimal cutoff value for baseline NLR being 4.76 in predicting severity and 4.88 in predicting organ failure in AP.[12]

Therefore, the objective of this study was to investigate the impact of different methods of determining inflammation criteria on diagnosing malnutrition based on the latest guidance from the GLIM working group. This was done to ascertain whether the new GLIM guidance on determining inflammatory status contributes to consistency in diagnosing malnutrition.

Materials and Methods

Research Population

This retrospective study included consecutive AP patients evaluated at the Affiliated Hospital of Chengde Medical University from June 2019 to January 2022. The Hospital Ethics Committee approved the study (CYFYLL2022256) and waived the requirement for patient-informed consent due to the study's retrospective nature. Inclusion criteria were as follows: (1) age ≥18 years, (2) diagnosis of AP according to the Atlanta Classification, (3) complete Nutrition Risk Screening 2002 (NRS2002) records and body mass index (BMI), Computer Tomography (CT), CRP, albumin and other relevant laboratory markers available. Patients were excluded if they were under 18 years old, pregnant, had chronic pancreatitis, lacked essential nutritional assessment data, or had an admission duration of less than 48 hours. The inclusion and exclusion criteria for this study are shown in Figure 1.

Defining Disease-Based GLIM Criteria and IM-Based GLIM Criteria

Our study employed the NRS2002 as the first step in identifying patients at nutritional risk. The NRS2002 included disease severity, impaired nutritional status, and age. The NRS2002 score ranged from 0 to 7. A score of 3 or higher indicated that the patient was at nutritional risk.[13] Nutritional risk screening was conducted by trained nurses at the beginning of the patient's admission.

Patients identified as being at nutritional risk were further evaluated in the second step. The GLIM criteria consist of three phenotypic and two etiologic criteria. Malnutrition is diagnosed when at least one phenotypic criterion and one etiologic criterion are present.[6] The GLIM guidelines suggest that muscle mass should primarily be assessed using

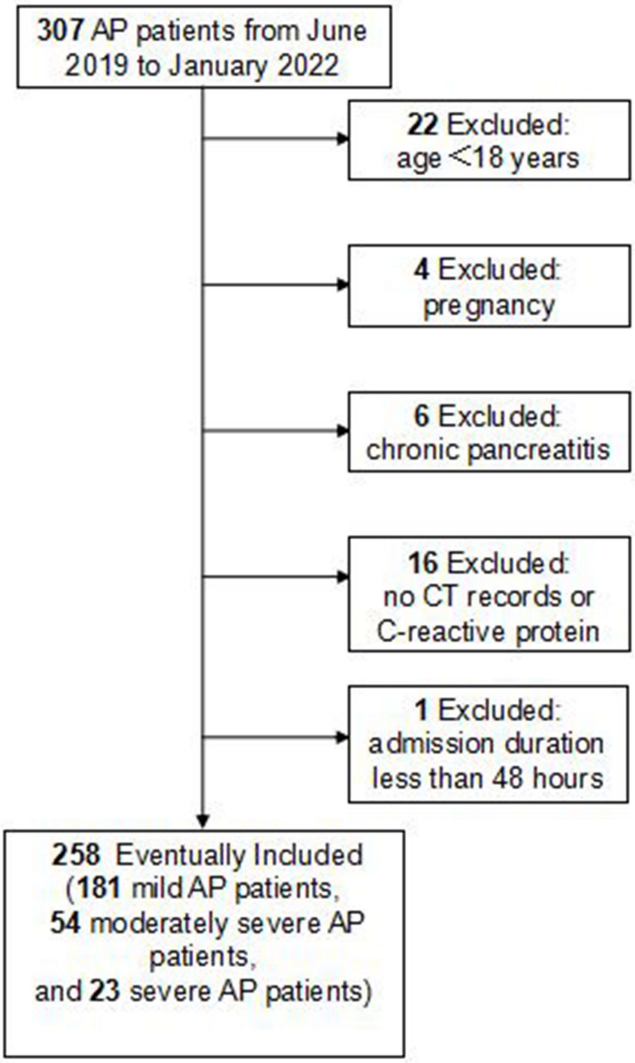

Figure 1 Flow chart of the study.
Abbreviations: AP, acute pancreatitis.

techniques like bioelectrical impedance, dual-energy X-ray absorptiometry, CT scans, and magnetic resonance imaging. Accordingly, we utilized the findings from our prior research, where a decrease in muscle mass was indicated by a CT-measured psoas muscle area (PMA) of 11.50 cm² or less in men and 8.22 cm² or less in women.[14] Etiologic criteria encompass reduced food intake or assimilation, as well as disease burden or inflammation. We assessed patients for reduced food intake or assimilation based on symptoms such as eating difficulties, dysphagia, nausea, vomiting, diarrhea, constipation, abdominal pain, and specific diagnoses, including short bowel syndrome, pancreatic insufficiency, esophageal stricture, gastroparesis, and intestinal obstruction in the electronic medical records, as well as the data recorded in the NRS2002 records.

In terms of the inflammation criteria, we applied one disease-based GLIM criterion and four IM-based GLIM criteria. Following the original GLIM working group guidelines and the updated recommendations as of the end of 2023, the disease-based GLIM criteria (original GLIM criteria) classified all patients with AP as meeting inflammatory criteria. The four IM-based GLIM criteria utilized the cutoffs from the literature, which were CRP ≥3 mg/L, albumin <35 g/L, NLR >4.9, and CAR >7.5 upon admission. These indicators were chosen for their feasibility in primary care settings. Given the retrospective nature of the study, these indicators had complete data for all patients.

Clinical Outcomes

As there was one patient death in total, we defined the composite outcome as a combination of death, complications (including local, systemic, and infectious complications), and organ failure. Additionally, we considered various complications, organ failure, LOS, and hospitalization costs as clinical outcomes, respectively. The definitions of local complications, systemic complications, organ failure, and the etiology of AP were based on the 2012 revised Atlanta Classification.[1] Infectious complications encompassed infectious shock, sepsis, septicemia, abdominal infection, severe pneumonia, infective endocarditis, and a procalcitonin level ≥ 25 ng/mL (excluding renal failure) when the aforementioned diagnoses were not present.

Nutrition-Related Indicators and Other Baseline Characteristics

Upon admission, physical measurements (including height and weight) were routinely conducted on the patients. Laboratory tests including CRP, neutrophil count, lymphocyte count, hemoglobin, glucose, triglyceride, cholesterol, albumin, corrected serum calcium (CsCa), creatinine, and urea, were performed within 72 hours after admission. CsCa (mmol/L) = measured total calcium (mmol/L) + [40 - serum albumin (g/L)] × 0.02.[15] Comorbidities were scored using the updated Charlson Comorbidity Index.[16] Since some patients with AP due to cholelithiasis underwent gallstone surgery during their hospitalization, which can affect the patient's LOS and hospitalization costs, we also recorded this information.

Statistical Analysis

The normality of the data distribution was tested using the Kolmogorov–Smirnov test or the Shapiro–Wilk test, as appropriate. Continuous variables were presented as the median (interquartile range) and compared using Mann–Whitney *U*-tests. Categorical variables were presented as numbers (percentages) and compared using chi-squared or Fisher's exact tests, as appropriate. Cohen's kappa statistic (κ) assessed the agreement between original GLIM criteria and four IM-based GLIM criteria as follows: $\kappa > 0.80$ corresponds to "excellent", 0.61–0.80 to "substantial", 0.41–0.60 to "moderate", and < 0.41 to "poor to fair". Multivariate logistic regression and multiple linear regression analyses evaluated the adverse clinical outcomes in GLIM-defined malnourished AP patients. We performed a sensitivity analysis by changing different cutoffs to assess whether and how the alteration of the cutoff changes the results. All statistical analyses were conducted using SPSS 20 (IBM, USA), with two-tailed p-values < 0.05 considered statistically significant.

Results

Validation of Indicator Cutoffs for Defining GLIM Inflammatory Criteria

Given that the cutoff value for CRP was suggested by the GLIM panel and the criterion for low albumin was <35 g/L, no further validation was performed. As there was currently no standardized cutoff value for NLR and CAR, a cutoff of NLR > 4.9[11,12] and CAR > 7.5[10] was established based on existing studies and verified. The validation of these cutoffs is presented in Table 1. As described in the literature, NLR > 4.9 effectively distinguished organ failure in AP, whereas CAR > 7.5 effectively differentiated SAP. Moreover, CAR reliably discriminated all adverse outcomes defined in this study. NLR also effectively differentiated among local complications, composite outcomes, LOS, and hospitalization costs. Therefore, the cutoff values of these two IMs will be adopted in the following research. In addition, CAR could effectively differentiate all the adverse outcomes we defined. NLR could also effectively differentiate between local complications, composite outcomes, LOS, and hospitalization costs. Therefore, the cutoff values of these two IMs were adopted in the next study.

Patients' Baseline Clinical Data

Table 2 presents the clinical characteristics of the patients at baseline. A total of 156 patients (60.47%) were identified as being at nutritional risk and 37 (14.34%) were classified as malnourished using the original GLIM criteria. When applying the four IM-based GLIM criteria, the prevalence of malnutrition ranged from 17 (6.59%) patients (CAR-based) to 32 (12.40%) patients (NLR-based), all of which were lower than the original GLIM criteria. The malnourished group

Table 1 Validation of Cutoff Values in Patients with Acute Pancreatitis [n (%), M (Q1, Q3)]

	NLR>4.9 (n=185)	NLR≤4.9 (n=73)	*P*	CAR>7.5 (n=13)	CAR≤7.5 (n=245)	*P*
Severe acute pancreatitis	18(9.7)	5(6.8)	0.629	8(61.5)	15(6.1)	<0.001
Length of stay (days)	10(7.0, 13.0)	7(5.0,10.0)	0.001	14(8.5,18.5)	9(7.0,12.0)	0.032
Hospitalization costs (yuan)	10232.08(7339.09,17,282.66)	8039.96(4780.52,12,353.46)	0.001	19,764.44(14,001.62,77,331.01)	9258.22(6473.38,14,529.64)	0.001
Infectious complications	16(8.6)	2(2.7)	0.093	7(53.8)	11(4.5)	<0.001
Local complications	38(20.5)	7(9.6)	0.037	8(61.5)	37(15.1)	<0.001
Organ failure	37(20.0)	6(8.2)	0.022	10(76.9)	33(13.5)	<0.001
Systemic complications	19(10.3)	5(6.8)	0.394	8(61.5)	16(6.5)	<0.001
Composite outcome	64(34.6)	12(16.4)	0.004	11(84.6)	65(26.5)	<0.001

Abbreviations: CAR, C-reactive protein /albumin ratio; NLR, neutrophil/lymphocyte ratio.

was on average more than 10 years older than the non-malnourished group across all five criteria. Additionally, laboratory nutritional indices such as total cholesterol and hemoglobin showed significant differences between the malnourished and non-malnourished groups. Albumin levels were also significantly different between the malnourished and non-malnourished groups across all four GLIM criteria except for those based on NLR. Triglycerides were found to be significantly different between the malnourished and non-malnourished groups under all four GLIM criteria except for those based on CRP.

Malnutrition and Clinical Outcomes Under Different GLIM Criteria

Since low BMI, low PMA, reduced intake, and weight loss were part of GLIM, we did not treat them as confounding variables to prevent incorporation bias. We adjusted for sex, age, overweight/obesity, comorbidity scores, and etiology in a multivariate logistic regression analysis.

Table 3 presents the risks of various adverse outcomes in malnourished patients according to the original GLIM criteria and four IM-based GLIM criteria. After adjusting for confounders, malnutrition under the original GLIM criteria was associated with infectious complications (OR: 3.937, 95% CI: 1.041 to 14.894) and local complications (OR: 3.623, 95% CI: 1.445 to 9.084). Malnutrition under all five GLIM criteria was associated with local complications and not with organ failure. Malnutrition under CRP- and CAR-based GLIM criteria was also associated with infectious complications and composite outcomes. Whereas malnutrition under albumin-based GLIM criteria was associated with all adverse outcomes except organ failure.

Table 4 shows the LOS and hospitalization costs for malnourished patients defined according to the original GLIM criteria and the four IM-based GLIMs. Under all four criteria, except the original GLIM, the LOS of malnourished patients was longer than that of non-malnourished patients, and the difference was statistically significant, ranging from approximately 3 days (NLR, 95% CI: 0.26 to 5.65) to 4.6 days (albumin, 95% CI: 1.46 to 7.82). Only under CRP- and albumin-based GLIM criteria, the hospitalization cost was higher in malnourished patients than in non-malnourished patients, with a statistically significant difference of 13408.81 (95% CI: 675.04 to 26142.57) to 21674.97 (95% CI: 6960.61 to 3689.34) yuan, respectively.

Sensitivity Analysis of GLIM Criteria Based on Different NLR and CAR Cutoffs

Since there were no recognized cutoff values for NLR and CAR, we performed sensitivity analyses of their cutoff values in multivariate logistic regression and multiple linear regression. We selected data 4.6,[17] 4.7,[11] and 4.8[12] from the literature as cutoff values for NLR. As for CAR, due to no literature data available, we obtained cutoff values of 4.5, 3.4, 3.4, 5.0, 5.0, and 0.8 for composite outcomes, systemic complications, SAP, organ failure, infectious complications, and local complications, respectively, based on the Youden index.

The various results obtained under the GLIM criteria defined by all NLR cutoffs showed little difference, which suggests that the results were robust. CAR, on the other hand, had slightly variable results under various cutoff values due to the more dispersed cutoff values. The results were robust in terms of composite outcomes, local complications, infectious complications, and length of stay. Whereas on systemic complications, organ failure, and SAP, the application

Table 2 Baseline Clinical Characteristics of Patients with Malnourished Acute Pancreatitis Under GLIM Criteria Based on Different Disease Burden/Inflammatory Markers [n (%), M (Q1, Q3)]

	All patients	Original GLIM		CRP-based GLIM		Albumin-based GLIM		NLR-based GLIM		CAR-based GLIM	
	(n=258)	malnourished	*P*	malnourished	*P*	malnourished	*P*	malnourished	*P*	malnourished	*P*
Incidence of malnutrition	-	37(14.34)	-	29(11.24)	-	20(7.75)	-	32(12.40)	-	17(6.59)	-
Male	153(59.3)	19(51.4)	0.287	17(58.6)	0.937	11(55.0)	0.683	16(50.0)	0.252	9(52.9)	0.581
Age (years)	49(37.75,64.25)	61(46.50,79.50)	0.001	58(45.00,74.00)	0.018	61(51.00,76.00)	0.011	60(45.75,76.25)	0.003	66(55.50,79.50)	0.002
Comorbidity score	0(0,0)	0(0,0)	0.498	0(0,0)	0.752	0(0,0)	0.969	0(0,0)	0.259	0(0,0)	0.713
Acute pancreatitis history, n (%)	75(29.1)	15(40.5)	0.097	10(34.5)	0.496	7(35.0)	0.543	12(37.5)	0.262	5(29.4)	1.000
Etiology, n (%)			0.310		0.675		0.218		0.181		0.046
Biliary	69(26.7)	14(37.8)		8(27.6)		5(25.0)		13(40.6)		5(29.4)	
Hypertriglyceridemic	46(17.8)	4(10.8)		4(13.8)		3(15.0)		3(9.4)		1(5.9)	
Alcoholic	76(29.5)	9(24.3)		7(24.1)		3(15.0)		7(21.9)		2(11.8)	
Other	67(26.0)	10(27.0)		10(34.5)		9(45.0)		9(28.1)		9(52.9)[a]	
Gallstone surgery during hospitalization	23(8.9)	4(10.8)	0.754	4(13.8)	0.306	3(15.0)	0.401	3(9.4)	1.000	2(11.8)	0.654
Overweight/obesity	172(66.7)	9(24.3)	<0.001	9(31.0)	<0.001	8(40.0)	0.008	8(25.0)	<0.001	6(35.3)	0.005
BMI, kg/m^2	25.50(23.00,27.78)	19.92(17.96,24.18)	<0.001	21.60(18.25,26.01)	<0.001	22.88(18.73,27.17)	0.009	20(17.68,24.82)	<0.001	22.04(18.98,27.78)	0.007
PMA, cm^2											
Male	19.19(15.55,23.51)	13.17(9.90,16.77)	<0.001	13.17(9.63,17.37)	<0.001	13.86(9.26,18.43)	0.002	12.64(9.92,17.67)	<0.001	15.26(9.08,18.43)	0.012
Female	10.91(8.58,12.89)	7.78(6.87,8.24)	<0.001	7.78(6.90,8.04)	<0.001	7.78(7.00,7.82)	<0.001	7.78(6.82,8.13)	<0.001	7.78(6.90,8.03)	<0.001
C-reactive protein (mg/L)	64.23(12.88,139.75)	22.66(1.46,144.84)	0.697	101.14(13.98,201.38)	0.061	130.08(7.52,221.65)	0.099	23.24(1.58,149.00)	0.867	130.38(4.42,267.04)	0.090
Albumin (g/L)	42.15(37.60,44.80)	37.77(34.80,44.35)	0.007	37.77(33.30,44.75)	0.012	34.80(30.20,41.25)	<0.001	40.04(36.00,44.80)	0.092	36.29(34.02,43.96)	0.008
CAR	1.54(0.30,3.55)	0.44(0.04,4.68)	0.894	2.29(0.35,5.80)	0.033	3.72(0.20,6.82)	0.037	0.50(0.04,4.45)	0.975	3.22(0.11,8.14)	0.064
Hemoglobin (g/L)	151.00(134.00,166.00)	139.00(119.00,154.00)	<0.001	140.00(124.00,158.00)	0.005	131.00(110.00,150.50)	<0.001	137.00(113.25,153.25)	<0.001	129.00(116.50,147.00)	<0.001
Neutrophil count ($\times 10^9$/L)	9.70(6.90,12.48)	6.96(5.52,9.56)	<0.001	8.59(5.37,10.22)	0.015	6.14(4.57,9.00)	0.001	7.60(6.20,9.70)	0.009	6.27(5.11,9.00)	0.006
Lymphocyte count ($\times 10^9$/L)	1.24(0.80,1.89)	1.02(0.75,1.32)	0.057	1.09(0.78,1.50)	0.208	1.24(0.88,1.89)	0.983	0.94(0.74,1.24)	0.006	1.24(0.91,1.88)	0.999
NLR	7.83(4.63,12.92)	7.60(4.31,12.98)	0.458	7.60(3.98,14.42)	0.513	4.84(3.28,8.21)	0.022	8.08(5.46,14.57)	0.653	5.06(3.66,8.08)	0.035
Blood glucose (mmol/L)	8.03(6.61,10.70)	7.30(5.64,9.82)	0.091	7.30(5.64,10.72)	0.271	7.05(5.46,11.13)	0.248	7.19(5.78,9.73)	0.112	5.98(5.26,10.33)	0.076
Total cholesterol (mmol/L)	4.83(3.88,6.50)	4.44(3.12,4.97)	0.012	4.06(2.93,5.55)	0.023	3.52(2.89,4.92)	0.012	4.46(3.33,4.98)	0.043	3.2(2.84,4.46)	0.004
Triglycerides (mmol/L)	2.35(1.17,6.57)	1.17(0.92,1.99)	0.001	1.49(1.04,4.22)	0.054	1.32(0.90,1.90)	0.032	1.16(0.92,2.03)	0.002	1.15(0.76,1.86)	0.011
CsCa (mmol/L)	2.20(2.10,2.25)	2.22(2.08,2.24)	0.507	2.21(2.02,2.24)	0.936	2.22(2.14,2.26)	0.291	2.22(2.06,2.24)	0.509	2.23(2.08,2.28)	0.370
Creatinine (μmol/L)	59.60(48.20,75.58)	60.90(53.10,80.40)	0.450	62.20(55.40,93.15)	0.137	61.55(54.72,93.98)	0.333	61.55(55.02,83.00)	0.283	62.20(56.60,101.40)	0.179
Urea (mmol/L)	4.93(3.98,6.58)	5.70(3.32,8.66)	0.203	6.55(3.32,9.20)	0.157	5.92(3.09,8.73)	0.418	5.91(3.69,8.73)	0.090	6.55(3.49,8.66)	0.176

Notes: Only hemoglobin was normally distributed in all groups under all criteria, the rest of the continuous variables were not normally distributed, so all continuous variables are expressed as medians. [a] Differences exist between the two groups.

Abbreviations: BMI, body mass index; CAR, C-reactive protein /albumin ratio; CRP, C-reactive protein; CsCa, corrected serum calcium; GLIM, Global Leadership Initiative on Malnutrition; NLR, neutrophil/lymphocyte ratio; PMA, psoas muscle area.

Table 3 Multivariate Logistic Regression Analysis of Malnutrition and Different Clinical Outcomes in Patients with Acute Pancreatitis Under Different GLIM Criteria

	Original GLIM		C-reactive protein-based GLIM		Albumin-based GLIM		NLR-based GLIM		CAR-based GLIM	
	OR (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*
Severe acute pancreatitis	2.081(0.607~7.136)	0.244	2.725(0.820~9.052)	0.102	4.775(1.380~16.514)	<0.001	1.071(0.262~4.371)	0.002	2.688(0.620~11.650)	0.001
Infectious complications	3.937(1.041~14.894)	0.044	5.451(1.489~19.965)	0.010	12.046(2.958~49.062)	0.001	2.921(0.727~11.743)	0.131	5.994(1.245~28.843)	0.025
Local complications	3.623(1.445~9.084)	0.006	5.627(2.199~14.397)	<0.001	6.431(2.203~18.771)	0.001	3.970(1.540~10.232)	0.004	8.471(2.582~27.796)	<0.001
Organ failure	1.542(0.547~4.346)	0.412	2.086(0.748~5.813)	0.160	2.882(0.950~8.746)	0.062	1.063(0.343~3.292)	0.915	2.857(0.848~9.627)	0.090
Systemic complications	1.839(0.550~6.152)	0.322	2.481(0.765~8.045)	0.130	4.449(1.316~15.045)	0.016	0.956(0.237~3.845)	0.949	2.550(0.603~10.784)	0.203
Composite outcome	1.660(0.726~3.794)	0.229	2.597(1.109~6.084)	0.028	3.127(1.178~8.302)	0.022	1.553(0.656~3.672)	0.317	3.969(1.364~11.543)	0.011

Note: Adjusted for age, sex, co-morbidity score, overweight/obesity, and etiology.

Abbreviations: CAR, C-reactive protein /albumin ratio; GLIM, Global Leadership Initiative on Malnutrition; NLR, neutrophil/lymphocyte ratio.

https://doi.org/10.2147/IJGM.S485400 DovePress

Table 4 Multiple Linear Regression Analysis of Malnutrition with the Length of Stay and Hospitalization Costs Under Different GLIM Criteria

	Length of stay (days)		Hospitalization costs (yuan)	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Original GLIM	2.21(−0.38~4.80)	0.094	9491.20(−2489.34~21,471.74)	0.120
C-reactive protein-based GLIM	3.29(0.55~6.03)	0.019	13,408.81(675.04~26,142.57)	0.039
Albumin-based GLIM	4.64(1.46~7.82)	0.004	21,674.97(6960.60~36,389.34)	0.004
NLR-based GLIM	2.96(0.26~5.65)	0.031	8081.87(−4460.71~20,624.45)	0.206
CAR-based GLIM	4.58(1.11~8.04)	0.010	11,984.99(−4207.10~28,177.07)	0.146

Note: Adjusted for age, sex, co-morbidity score, overweight/obesity, etiology, and gallstone surgery.
Abbreviations: CAR, C-reactive protein /albumin ratio; GLIM, Global Leadership Initiative on Malnutrition; NLR, neutrophil/lymphocyte ratio.

Table 5 Agreement of Different GLIM Criteria Compared to the Original GLIM Criteria

	κ
C-reactive protein-based GLIM	0.861
Albumin-based GLIM	0.668
NLR-based GLIM	0.916
CAR-based GLIM	0.593

Abbreviations: CAR, C-reactive protein /albumin ratio; GLIM, Global Leadership Initiative on Malnutrition; NLR, neutrophil/lymphocyte ratio.

of 3.4, 4.5, and 5.0 as CAR cutoff-defined GLIM criteria made the results statistically significant; on hospitalization costs, all four other CAR cutoff-defined GLIM criteria made the otherwise nonsignificant results statistically significant. This suggests the possibility that appropriately downwardly adjusted CAR cutoff values may have stronger predictive value for AP patients. See Supplementary Table 1.

Comparison of Agreement Between Four IM-Based GLIM Criteria and the Original GLIM Criteria

Table 5 displays the agreement of the four IM-based GLIM criteria compared to the original GLIM criteria. The κ values of the four GLIM criteria remained consistent with the high and low prevalence of malnutrition when each criterion was applied independently. Among the criteria, the NLR- and CRP-based GLIM criteria demonstrated excellent agreement with the original GLIM criteria.

Discussion

Inflammation can lead to malnutrition, which is why the GLIM working group uses inflammation as an etiologic criterion, alongside reduced intake. In acute and chronic inflammation, the sympathetic nervous system, the immune system, and the hypothalamic–pituitary–adrenal axis are activated, stress hormones (including cortisol and catecholamines) are released, and glycogenolysis and gluconeogenesis in the liver are increased. Pro-inflammatory cytokines are released, including interleukin 6 (IL-6), interleukin 1β (IL-1β), and tumor necrosis factor α. These pro-inflammatory cytokines directly contribute to protein degradation and affect the brain pathways controlling food intake, resulting in delayed gastric emptying and increased skeletal muscle catabolism. In addition, pro-inflammatory cytokines (mainly IL-6 and IL-1β) interact with glucagon-like peptide-1 released from intestinal tissues, leading to reduced food intake and unintentional weight loss. Combining these mechanisms leads to impaired metabolism and a hypermetabolic state, ultimately resulting in malnutrition.[18]

AP patients are prone to malnutrition, which is associated with decreased intake, increased energy needs, and inflammation. Combined malnutrition in AP patients is associated to higher mortality, severe sepsis, infectious shock, respiratory failure, longer LOS, and higher hospitalization costs.[19,20] However, previous studies in AP lacked uniform criteria for defining malnutrition. Our study validated the GLIM criteria for the first time in AP and confirmed the impact of GLIM-defined malnutrition on AP prognosis. However, due to the use of five different criteria for inflammation in our study, the results varied.

Accurate data on the prevalence of malnutrition among AP patients are not readily available. We found a malnutrition prevalence of 14.34% based on the original GLIM criteria, in contrast to 6.59%-12.40% for the other four criteria, which might underestimate the actual prevalence, particularly the criteria based on the CAR. There was no standardized cutoff value for CAR, and the value used in our study was derived from previous literature and was well-validated in our specific AP population. However, this choice might result in an overestimation of the cutoff value, sacrificing sensitivity for specificity and the predictive capability of adverse outcomes.

In our study, we discovered that hemoglobin, albumin (excluding the NLR-based GLIM), triglycerides (excluding the CRP-based GLIM), and cholesterol levels were lower in malnourished patients compared to non-malnourished individuals across all five GLIM criteria. The assessment of protein malnutrition in clinical settings often involves laboratory tests for serum proteins such as albumin and hemoglobin. Additionally, decreased total cholesterol levels are commonly used as an indicator of insufficient energy intake. A systematic review published in 2017 highlighted that albumin, prealbumin, hemoglobin, total cholesterol, and total protein serve as valuable biomarkers for adult malnutrition.[21] Furthermore, Demir et al observed that malnourished patients identified through subjective global assessment (SGA) exhibited lower levels of cholesterol, triglycerides, and albumin in comparison to well-nourished patients.[22] This finding suggested that the laboratory parameters for malnutrition diagnosis based on GLIM and other criteria, including SGA, were consistent.

As a diagnostic criterion for malnutrition, the GLIM criteria are not primarily used to predict outcomes such as mortality or complications, but malnutrition is one of the important factors influencing outcomes. Furthermore, the GLIM working group's 2020 guidelines for the validation of GLIM criteria stated that predicting adverse outcomes was a form of criterion validity, particularly when the gold standard was not available.[23] There have been numerous studies on the predictive utility of GLIM in various diseases, with the majority focusing on cancer patients. The GLIM criteria proved effective in predicting mortality or survival in cancer patients, and malnutrition as defined by GLIM was associated with an increased risk of complications, longer LOS, and poorer quality of life in cancer patients.[24–28] A systematic review and meta-analysis that included cancer and critically ill patients, medical and surgical patients, demonstrated that malnutrition diagnosed by GLIM was associated with an increased risk of death within one year and beyond.[29] GLIM has also shown good predictive utility in patients with other diseases, such as chronic liver disease and heart failure.[30,31] Moreover, malnutrition defined by GLIM was associated with mortality in both hospitalized elderly patients and the elderly in the community.[7,32] However, there were differing conclusions regarding the predictive role of GLIM. For instance, Okada et al found that malnutrition diagnosed by GLIM was not a significant prognostic factor for overall survival in patients with esophageal cancer.[33] In studies on ICU patients, the prediction of LOS and mortality risk by GLIM was controversial.[34,35]

Due to the low mortality rate in our study, we opted for alternative outcomes. Our study revealed that both the original GLIM and all four IM-based GLIMs predicted a three- to eight-fold increase in the rate of local complications among malnourished patients. Additionally, all GLIMs, excluding the NLR-based one, projected a four- to twelve-fold rise in infectious complications among malnourished patients. Furthermore, all criteria, apart from the original GLIM, anticipated an increase of three to four days in LOS for malnourished patients. Notably, even though the albumin-based GLIM only identified approximately half of the malnourished patients in the original GLIM, it was associated to all adverse outcomes, including LOS and hospitalization costs, except for organ failure. Moreover, it demonstrated superior predictive power compared to the original GLIM criteria. On the other hand, the NLR-based GLIM, although it closely identified malnourished patients similar to the original GLIM, did not correlate with all adverse outcomes except for local complications. This discrepancy could be attributed to the chosen cutoff value of the NLR. Like CAR, we adopted cutoff values from existing literature; however, contrary to CAR, the cutoff values for NLR might have

been underestimated, leading to its high sensitivity. Despite its high specificity (compared to the original GLIM criteria), the NLR's predictive capability for adverse outcomes was weak, resembling that of the original GLIM criteria.

Our conclusions were similar to those of Xie et al, who found that the GLIM criteria based on CRP (≥5.1), NLR (≥4.59), and albumin (<37.6) better predicted long-term prognosis, short-term prognosis, LOS, and hospitalization costs in cancer patients compared to the original GLIM criteria. The original criteria stated that all cancer patients met the inflammation criteria, while the albumin-based GLIM criteria more effectively predicted long-term outcomes, and the CRP-based GLIM criteria were more effective in predicting short-term outcomes.[17]

The NLR-based GLIM criteria showed the best agreement with the original GLIM criteria, whereas the CAR- and albumin-based GLIM criteria showed moderated to substantial agreement with the original GLIM criteria, despite their corresponding good predictive utility. The inconsistency between GLIM criteria based on disease burden and various IMs was significant, and using different standards can lead to significant differences in diagnostic results. This suggests the following: Firstly, while GLIM can predict adverse outcomes, it may be less robust than objective inflammation criteria or specialized predictors. Secondly, the inconsistency in malnutrition rates and the predictive effectiveness for clinical outcomes of GLIM criteria, as defined by different IMs, is partly attributed to the selection of IMs and their cutoff values. Hence, there is a necessity to determine the optimal IM in GLIM criteria. Thirdly, not all AP patients may fulfill the GLIM criteria for inflammation. It is subjective to assume that all diseases are inflammatory when IMs serve as objective indicators, making it challenging to precisely align the two. Finally, the diagnostic criteria for malnutrition in the past were mostly subjective judgments, and as the latest diagnostic standard for malnutrition, GLIM's superiority over the old standards should not only lie in its convenience, but also in its reliability, that is, it should rely more on objective indicators and not be affected by subjective factors.

There are certain limitations to this study. Firstly, as this was a retrospective study conducted in a single institution, there is a possibility of selection bias. Secondly, there were few studies on different IMs in GLIM, and the cutoff values were not standardized. This lack of standardization may partly account for the discrepancies in outcomes when various GLIM criteria are used to define malnutrition. However, sensitivity analyses demonstrated the robustness of the results and further confirmed the stronger predictive value of the IM-based GLIM criteria than the original GLIM criteria for the prognosis of AP patients. Furthermore, due to baseline discrepancies in age and overweight/obesity between malnourished and non-malnourished groups under each criterion, it is conceivable that the clinical predictive value of malnutrition definitions under each criterion was more consistent in subgroups. The GLIM criteria defined by different IMs may also show better agreement with the original GLIM criteria in subgroups.

Conclusion

This study provides the first validation of the GLIM criteria in AP patients. Malnourished AP patients are more prone to local complications than non-malnourished patients. Nonetheless, variations in different disease burden/IMs could impact nutritional assessment. IM-based GLIM criteria have stronger predictive value than the original GLIM criteria in assessing prognosis in AP patients, and the albumin-based GLIM criteria demonstrate the strongest predictive utility. The inflammatory criteria within the GLIM criteria may require further refinement.

Abbreviations

AP, acute pancreatitis; BMI, body mass index; CAR, C-reactive protein /albumin ratio; CRP, C-reactive protein; CsCa, corrected serum calcium; CT, Computer Tomography; GLIM, Global Leadership Initiative on Malnutrition; ICU, intensive care unit; IM, inflammatory marker; LOS, length of stay; NLR, neutrophil/lymphocyte ratio; PMA, psoas muscle area; SAP, severe acute pancreatitis; SGA, subjective global assessment.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Affiliated Hospital of Chengde Medical University (No. CYFYLL2022256). The ethics committee waived the requirement for written informed consent because of the retrospective nature of the study. Before analysis, identifying information was removed to protect patient confidentiality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was conducted as a project of the Hebei Medical Science Research Program (Project No. 20231379). It received no specific grant from public, commercial, or not-for-profit funding agencies.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102–111. doi:10.1136/gutjnl-2012-302779
2. Canamares-Orbis P, Garcia-Rayado G, Alfaro-Almajano E. Nutritional support in pancreatic diseases. *Nutrients*. 2022;14(21):4570. doi:10.3390/nu14214570
3. Giner M, Laviano A, Meguid MM, Gleason JR. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. *Nutrition*. 1996;12(1):23–29. doi:10.1016/0899-9007(95)00015-1
4. Tangvik RJ, Tell GS, Eisman JA, et al. The nutritional strategy: four questions predict morbidity, mortality and health care costs. *Clin Nutr*. 2014;33(4):634–641. doi:10.1016/j.clnu.2013.09.008
5. Dumont C, Wuestenberghs F, Lanthier N, Piessevaux H, Dahlqvist G. Malnutrition is highly prevalent in hospitalized cirrhotic patients and associates with a poor outcome. *Acta gastro-enterologica Belgica*. 2022;85(2):311–319. doi:10.51821/85.2.9016
6. Cederholm T, Jensen GL, Correia M, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *J Cachexia Sarcopenia Muscle*. 2019;10(1):207–217. doi:10.1002/jcsm.12383
7. Cederholm T, Barazzoni R. Validity and feasibility of the global leadership initiative on malnutrition diagnostic concept in older people: a literature review from August 2021 to August 2022. *Curr Opin Clin Nutr Metab Care*. 2023;26(1):23–31. doi:10.1097/mco.0000000000000886
8. Cederholm T, Jensen GL, Ballesteros-Pomar MD, et al. Guidance for assessment of the inflammation etiologic criterion for the GLIM diagnosis of malnutrition: a modified Delphi approach. *Clin Nutr*. 2023. doi:10.1016/j.clnu.2023.11.026
9. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and Clinical Significance. *JPEN J Parenter Enteral Nutr*. 2019;43(2):181–193. doi:10.1002/jpen.1451
10. Piñerúa-Gonsálvez JF, Ruiz Rebollo ML, Zambrano-Infantino RDC, Rizzo-Rodríguez MA, Fernández-Salazar L. Value of C-reactive protein/albumin ratio as a prognostic marker of acute pancreatitis: a retrospective study. *Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva*. 2023;115. doi:10.17235/reed.2023.9345/2022
11. Azab B, Jaglall N, Atallah JP, et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. *Pancreatology*. 2011;11(4):445–452. doi:10.1159/000331494
12. Jeon TJ, Park JY. Clinical significance of the neutrophil-lymphocyte ratio as an early predictive marker for adverse outcomes in patients with acute pancreatitis. *World J Gastroenterol*. 2017;23(21):3883–3889. doi:10.3748/wjg.v23.i21.3883
13. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321–336. doi:10.1016/s0261-5614(02)00214-5
14. Fu H, Li P, Xing Q, Jiang H, Sui H. Cutoff value of psoas muscle area as reduced muscle mass and its association with acute pancreatitis in China. *Int J Gene Med*. 2023;16:2733–2751. doi:10.2147/ijgm.S413308
15. Jain A, Bhayana S, Vlasschaert M, House A. A formula to predict corrected calcium in haemodialysis patients. *Nephrology, Dialysis, Transplantation: Official publication of the European Dialysis and Transplant Association - European Renal Association*. 2008;23(9):2884–2888. doi:10.1093/ndt/gfn186
16. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–682. doi:10.1093/aje/kwq433
17. Xie H, Yuan K, Ruan G, et al. Improving the assessment of malnutrition in cancer: using systemic inflammation markers as a supplement to the inflammation items of the GLIM criteria. *Clin Nutr*. 2023;42(10):2036–2044. doi:10.1016/j.clnu.2023.08.020
18. Stumpf F, Keller B, Gressies C, Schuetz P. Inflammation and nutrition: friend or foe? *Nutrients*. 2023;15(5):1159. doi:10.3390/nu15051159

19. Thavamani A, Umapathi KK, Sferra TJ, Sankararaman S. Undernutrition and obesity are associated with adverse clinical outcomes in hospitalized children and adolescents with acute pancreatitis. *Nutrients*. 2020;13(1):43. doi:10.3390/nu13010043
20. Le A, Shaikh A, Ali M, Khrais A, Abboud Y. Malnutrition imparts worse outcomes in patients admitted for acute pancreatitis. *Cureus*. 2023;15(3): e35822. doi:10.7759/cureus.35822
21. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. *Nutrients*. 2017;9(8):829. doi:10.3390/nu9080829
22. Demir MV, Tamer A, Cinemre H, Uslan I, Yaylaci S, Erkorkmaz U. Nutritional status and laboratory parameters among internal medicine inpatients. *Niger J Clin Pract*. 2015;18(6):757–761. doi:10.4103/1119-3077.158145
23. Keller H, de van der Schueren MAE, Jensen GL, et al. Global Leadership Initiative on Malnutrition (GLIM): guidance on validation of the operational criteria for the diagnosis of protein-energy malnutrition in adults. *JPEN J Parenter Enteral Nutr*. 2020;44(6):992–1003. doi:10.1002/jpen.1806
24. Wang PP, Soh KL, Binti Khazaai H, et al. Nutritional assessment tools for patients with cancer: a narrative review. *Curr Med Sci*. 2024;44 (1):71–80. doi:10.1007/s11596-023-2808-4
25. Yin L, Chong F, Huo Z, Li N, Liu J, Xu H. GLIM-defined malnutrition and overall survival in cancer patients: a meta-analysis. *JPEN J Parenter Enteral Nutr*. 2023;47(2):207–219. doi:10.1002/jpen.2463
26. Matsui R, Rifu K, Watanabe J, Inaki N, Fukunaga T. Impact of malnutrition as defined by the GLIM criteria on treatment outcomes in patients with cancer: a systematic review and meta-analysis. *Clin Nutr*. 2023;42(5):615–624. doi:10.1016/j.clnu.2023.02.019
27. Peng D, Zong K, Yang H, et al. Malnutrition diagnosed by the global leadership initiative on malnutrition criteria predicting survival and clinical outcomes of patients with cancer: a systematic review and meta-analysis. *Frontiers in Nutrition*. 2022;9:1053165. doi:10.3389/fnut.2022.1053165
28. Matsui R, Rifu K, Watanabe J, Inaki N, Fukunaga T. Current status of the association between malnutrition defined by the GLIM criteria and postoperative outcomes in gastrointestinal surgery for cancer: a narrative review. *J Cancer Res Clin Oncol*. 2023;149(4):1635–1643. doi:10.1007/s00432-022-04175-y
29. Bian W, Li Y, Wang Y, et al. Prevalence of malnutrition based on global leadership initiative in malnutrition criteria for completeness of diagnosis and future risk of malnutrition based on current malnutrition diagnosis: systematic review and meta-analysis. *Frontiers in Nutrition*. 2023;10:1174945. doi:10.3389/fnut.2023.1174945
30. Miwa T, Hanai T, Nishimura K, et al. Usefulness of the Global Leadership Initiative on Malnutrition criteria to predict sarcopenia and mortality in patients with chronic liver disease. *Hepatol Res*. 2022;52(11):928–936. doi:10.1111/hepr.13816
31. Oguri M, Ishii H, Yasuda K, Sumi T, Takahashi H, Murohara T. Combined prognostic value of malnutrition using GLIM criteria and renal insufficiency in elderly heart failure. *ESC Heart Failure*. 2022;9(1):704–711. doi:10.1002/ehf2.13685
32. Sánchez-Rodríguez D, De Meester D, Minon L, et al. Association between malnutrition assessed by the global leadership initiative on malnutrition criteria and mortality in older people: a scoping review. *Int J Environ Res Public Health*. 2023;20(7):5320. doi:10.3390/ijerph20075320
33. Okada G, Matsumoto Y, Habu D, Matsuda Y, Lee S, Osugi H. Relationship between GLIM criteria and disease-specific symptoms and its impact on 5-year survival of esophageal cancer patients. *Clin Nutr*. 2021;40(9):5072–5078. doi:10.1016/j.clnu.2021.08.008
34. Díaz G, Tdc MI, Gonzalez MC, Reyes M. The global leadership initiative on malnutrition criteria for the diagnosis of malnutrition in patients admitted to the intensive care unit: a systematic review and meta-analysis. *Clin Nutr*. 2023;42(2):182–189. doi:10.1016/j.clnu.2022.12.007
35. Milanez DSJ, Razzera EL, Lima J, Silva FM. Feasibility and criterion validity of the GLIM criteria in the critically ill: a prospective cohort study. *JPEN J Parenter Enteral Nutr*. 2023;47(6):754–765. doi:10.1002/jpen.2536