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ORIGINAL RESEARCH

Validation of the Global Leadership Initiative on Malnutrition Criteria for Predicting Adverse Outcomes in Acute Pancreatitis

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Background and Aim: The Global Leadership Initiative on Malnutrition (GLIM) has proposed criteria for the diagnosis of malnutrition. No studies validated the GLIM criteria in acute pancreatitis (AP). The present study aimed to validate the predictive capacity of GLIM criteria for adverse outcomes in AP patients.

Patients and Methods: Clinical data of 269 patients with AP were analyzed retrospectively. The Nutritional Risk Screening 2002 (NRS2002) was chosen as the screening tool. Multivariate logistic regression analyses evaluated the adverse clinical outcomes in malnourished patients.

Results: Overall, 160 patients (59.5%) were at nutritional risk and 38 (14.1%) were malnourished. Reduced muscle mass/ low body mass index + inflammation combinations contributed most to malnutrition overall and in each subgroup. The malnourished group had lower hemoglobin, neutrophils, albumin, total cholesterol, and triglycerides than the well-nourished group. The malnourished group had higher hospitalization costs (CNY, 11319.34 vs 9258.22, p <0.001) and more local complications (34.2% vs 14.7%, p =0.009) than the well-nourished group. There was an interaction between malnutrition and overweight/obesity on local complications (p for interaction = 0.023). Multivariate logistic regression showed malnutrition was significantly associated with local complications (OR 12.2, 95% CI: 2.51–59.37), infectious complications (OR 9.95, 95% CI: 1.25–79.44) and composite adverse outcome (OR 4.78, 95% CI: 1.05–21.73) in the overweight/obesity subgroup. There was no association between malnutrition and the rate of various adverse outcomes in the non-overweight/obesity subgroup. Additionally, we observed an association between malnutrition and composite adverse outcome (OR 6.75, 95% CI: *1*.49–30.68) in patients <70 years only in females.

Conclusion: Malnourished AP patients were more likely to have adverse outcomes than well-nourished patients. Malnutrition was associated with various adverse outcomes only in the overweight/obesity subgroups.

Keywords: acute pancreatitis, complication, GLIM, nutrition assessment, obesity, prognosis

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 (MSAP) and severe AP (SAP), inflammatory and septic complications increase metabolism, energy requirements, and proteolytic metabolism. In addition, AP patients tend to eat less in the early stages of the disease because of abdominal pain. Therefore, all AP patients are related to a significant risk of malnutrition.[2] Malnutrition and the risk of malnutrition are associated with adverse outcomes, such as higher rates of complications, longer hospitalization, and increased mortality rates.[3–5] Therefore, assessing the nutritional status of AP patients is essential.

Because inconsistencies in the criteria used to evaluate nutritional status make it difficult to compare the effectiveness of nutritional interventions across studies, the Global Leadership Initiative on Malnutrition (GLIM) Working Group issued a global consensus recommendation in 2018 on the criteria for identifying malnutrition in adults.[6] The GLIM

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criteria consist of two steps: first, using any validated screening tool to identify nutritional risk status; second, conducting malnutrition diagnosis and severity grading (which should include at least one phenotypic criterion and one etiologic criterion). However, since it is an expert consensus, it must be tested in different populations to verify its validity. Studies validating GLIM have focused on patients with chronic diseases such as tumors. In contrast, fewer studies have been conducted on acute diseases, with no reports of GLIM being applied in AP.

The present study aimed to validate the predictive capacity of GLIM criteria for adverse outcomes in AP patients.

Materials and Methods

Study Design and Population

This retrospective study included consecutive AP patients evaluated at the Affiliated Hospital of Chengde Medical University from June 2019 to January 2022. The study protocol was approved by the Hospital Ethics Committee (CYFYLL2022256), which waived the requirement for patient-informed consent due to the study's retrospective nature. The study conformed to the principles of the Declaration of Helsinki. Inclusion criteria were as follows: (1) age ≥ 18 years old, (2) diagnosis of AP according to the Atlanta classification, and (3) complete Nutritional Risk Screening 2002 (NRS2002) screening records and body mass index (BMI), computer tomography (CT) were available. Patients were excluded if they were < 18 years old, pregnant, had chronic pancreatitis, or the duration of admission was less than 48 hours.

Nutritional Risk Screening

Our study used the NRS2002 as the first step in identifying patients at nutritional risk. The NRS2002 included disease severity (mild, moderate, or severe); impaired nutritional status based on BMI, weight loss, or decreased food intake; and age with a cutoff of 70 years old. The final NRS2002 score ranged from 0 to 7. A score of 3 to 7 indicated that the patient was at nutritional risk.[7] Nutritional risk screening was performed by trained nurses at the beginning of the patient's admission.

Validating GLIM in AP

Patients who screened positive in the first step underwent further evaluation. In the second step of the GLIM, phenotypic criteria included (1) involuntary weight loss, > 5% within six months or > 10% over six months; (2) low BMI in Asians, < 18.5 kg/m^2 if < 70 years old or < 20.0 kg/m^2 if ≥ 70 years old; and (3) reduced muscle mass, applying the results of our previous study, psoas muscle area (PMA) ≤ 11.50 cm^2 in men and ≤ 8.22 cm^2 in women.[8] Etiologic criteria included reduced food intake or assimilation, and disease burden or inflammation. We assessed patients for reduced food intake or assimilation through descriptions of eating, dysphagia, nausea, vomiting, diarrhea, constipation, or abdominal pain, and diagnoses of short bowel syndrome, pancreatic insufficiency, esophageal stricture, gastroparesis, and intestinal obstruction in the Hospital Information System medical records, as well as intake on the NRS2002 screening records. No patients had chronic gastrointestinal symptoms or diseases other than AP. Regarding the assessment of disease burden or inflammation in the process of GLIM diagnosis, a guidance paper by the GLIM working group has just been published. As stated in this guidance, all patients with AP had inflammatory status and fulfilled the GLIM disease burden/inflammation criterion.[9]

Since there was one patient death in total, we defined composite adverse outcome as a composite of death, complications (including local complications, systemic complications, and infectious complications), and organ failure. Local complications, systemic complications, organ failure, and the etiology of AP were defined in the 2012 revised Atlanta Classification. Infectious complications included infectious shock, sepsis, septicemia, abdominal infection, severe pneumonia, infective endocarditis, and a procalcitonin ≥ 25 ng/mL (excluding renal failure) in the absence of the above diagnoses.

We recorded the relevant laboratory tests and the Charlson comorbidity index. Of which corrected serum calcium (CsCa) (mmol/L) = measured total Ca (mmol/L) + [40 - serum albumin (g/L)] × 0.02.[10] Comorbidities were scored using the updated Charlson comorbidity index.[11]

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 expressed as the median (interquartile range) and compared using Mann–Whitney U-tests. Categorical variables were expressed as numbers (percentages) and compared using chi-squared or Fisher's exact tests, as appropriate. Cohen's kappa statistic (κ) assessed the agreement between GLIM criteria (any phenotypic criteria + any etiologic criteria) and different combinations of GLIM as follows: $\kappa > 0.80$ indicates "excellent"; 0.61–0.80 "substantial"; 0.41–0.60 "moderate"; and < 0.41 "poor to fair". Multivariate logistic regression analyses evaluated the adverse clinical outcomes in malnourished AP patients diagnosed by GLIM, and 95% confidence intervals (CI) were calculated. Interactions were used to examine whether the association between malnutrition and adverse clinical outcomes differed by other factors. All statistical analyses were performed using SPSS 20 (IBM, USA), with two-tailed p-values < 0.05 defined as statistically significant, except for the interaction analyses where p-values < 0.10 were used.

Results

Participants

We analyzed 269 AP patients with a median age of 49 (37–64) years, and 111 (41.3%) were female. There were 55 (20.4%) MSAP and 24 (8.9%) SAP. The most frequent etiology was alcohol in 78 (29%) cases, followed by cholelithiasis in 69 (25.7%) cases, high triglycerides in 47 (17.5%) cases, and other in 75 (27.9%) cases. All patients underwent NRS2002 screening. Overall, 160 patients (59.5%) were at nutritional risk and 38 (14.1%) were malnourished. The baseline characteristics, clinical outcomes, and hematologic parameters of the malnourished and well-nourished groups are shown in Table 1. Several baseline characteristics, clinical outcomes and nutritional parameters were statistically different between malnourished and well-nourished patients, such as an older age (61 vs 48, $p = 0.001$), lower BMI (19.92 vs 25.95, $p < 0.001$), higher hospitalization costs (CNY, 11319.34 vs 9258.22, $p < 0.001$), more local complications (34.2% vs 14.7%, $p = 0.009$), and lower values of nutritional biomarkers in malnourished patients. Due to the age and BMI in baseline characteristics were imbalanced between malnourished and well-nourished patients, we performed subgroup analyses. Infectious complications and composite adverse outcome were more frequent, and length of stay (LOS) was longer in the malnourished than the well-nourished patients in the <70 years subgroup, in addition to more local complications and hospitalization costs. While there was no statistically significant difference in the comparison of the various outcomes between the malnourished and well-nourished patients in the ≥70 years subgroup, and the LOS was even shorter in the malnourished group than in the well-nourished group (7 vs 10, p=0.05) (Table 2). Comparisons of various outcomes between the malnourished and well-nourished patients in the non-overweight/obesity subgroups were not statistically different, while the proportion of AP history was higher in the malnourished group than in the well-nourished group (44.8% vs 16.4%, p=0.008). In contrast, comparisons of various outcomes between the malnourished and well-nourished patients in the overweight/obesity subgroups were similar to those in the <70 years subgroup. In addition, the proportion of MSAP and SAP patients was higher in the overweight/obese subgroup (Table 3). In addition, we also conducted subgroup analyses according to aetiology. In the hypertriglyceridemic subgroup, all adverse outcomes (including LOS, hospitalization costs, and the proportion of SAP) were significantly higher between malnourished and well-nourished patients. However, no differences were seen in the other subgroups. See Supplementary Table 1.

Prevalence of GLIM Phenotypic and Etiologic Combinations

Table 4 describes the prevalence of the 21 phenotypic and etiologic combinations. The predominant GLIM combinations were GLIM 6: reduced muscle mass + inflammation (11.5%, 31/296), followed by GLIM 4: low BMI + inflammation (7%, 19/269). No patients fulfilled all three phenotypic criteria. Using any GLIM phenotypic criterion + any etiologic criterion combination as the reference method, there was a substantial association between the reduced muscle mass/low BMI + inflammation combinations and the reference method (κ=0.62 and 0.63, respectively). Across subgroups, it remained the combination of reduced muscle mass + inflammation and low BMI + inflammation that contributed most to the prevalence of malnutrition.

Table 1 The Baseline Characteristics, Clinical Outcomes, and Hematologic Parameters of All AP Patients and Malnourished AP Patients Identified by Global Leadership Initiative on Malnutrition Criteria

	Total (n = 269)	Malnourished (n = 38)	Well-Nourished (n = 231)	p
Female, n(%)	111(41.3)	19(50.0)	92(39.8)	0.287
Age, years	49(37.0–64.0)	61(46.5–79.5)	48(37.0–61.0)	**0.001**
AP history, n(%)	76(28.3)	15(39.5)	61(26.4)	0.119
Overweight/obesity, n(%)	179(66.5)	9(23.7)	170(73.6)	**<0.001**
BMI, kg/m^2	25.56(23.1–27.78)	19.92(17.96–24.18)	25.95(23.88–28.41)	**<0.001**
Comorbidity score	0(0–0)	0(0–0)	0(0–0)	0.288
Aetiology, n(%)				0.306
Biliary	69(25.7)	14(36.8)	55(23.8)	–
Hypertriglyceridemic	47(17.5)	4(10.5)	43(18.6)	
Alcoholic	78(29.0)	9(23.7)	69(29.9)	
Other	75(27.9)	11(28.9)	64(27.7)	
AP classification, n(%)				0.425
Mild	190(70.6)	24(63.2)	166(71.9)	–
Moderately severe	55(20.4)	9(23.7)	46(19.9)	
Severe	24(8.9)	5(13.2)	19(8.2)	
LOS, days	9(7.0–12.5)	9(6.5–14.5)	9(7.0–12.0)	0.535
Hospitalization costs, CNY	9273.22(6520.93–14,840.03)	11,319.34(8699.39–21,981.49)	9258.22(6632.98–15,221.06)	**0.011**
Infectious complications, n(%)	18(6.7)	5(13.2)	13(5.6)	0.150
Local complications, n(%)	47(17.5)	13(34.2)	34(14.7)	**0.009**
Organ failure, n(%)	45(16.7)	8(21.1)	37(16.0)	0.482
Systemic complications, n(%)	25(9.3)	5(13.2)	20(8.7)	0.369
Composite adverse outcome, n(%)	78(29.0)	14(36.8)	64(27.7)	0.253
CRP, mg/L	64.23(12.89–139.75)	22.66(1.47–144.84)	64.19(14.10–138.76)	0.697
Hemoglobin, g/L	152.00(134.25–165.00)	139.00(119.00–154.00)	153.00(137.00–166.00)	**<0.001**
Neutrophil count, $\times 10^9/L$	9.76(6.91–12.43)	6.96(5.52–9.56)	10.26(7.25–13.04)	**<0.001**
Lymphocyte count, $\times 10^9/L$	1.24(0.79–1.90)	1.02(0.75–1.33)	1.27(0.78–1.92)	0.057
Albumin, g/L	42.10(37.61–44.80)	37.77(34.80–44.35)	42.37(37.71–45.00)	**0.003**
Blood glucose, mmol/L	7.99(6.55–10.62)	7.30(5.65–9.83)	8.14(6.71–10.75)	0.143
Total cholesterol, mmol/L	4.84(3.88–6.46)	4.44(3.12–4.97)	5.01(3.94–6.74)	**0.005**
Triglycerides, mmol/L	2.41(1.17–6.62)	1.17(0.93–1.99)	3.12(1.31–8.09)	**0.001**
CsCa, mmol/L	2.20(2.10–2.25)	2.22(2.09–2.24)	2.18(2.10–2.25)	0.381
Creatinine, μmol/L	59.80(48.35–76.40)	60.90(53.10–80.40)	58.90(48.20–75.50)	0.413
Urea nitrogen, mmol/L	4.94(3.98–6.60)	5.70(3.33–8.66)	4.82(4.00–6.18)	0.163
Amylase, U/L	352.30(134.50–870.40)	394.30(203.65–704.40)	343.00(128.70–914.20)	0.527
Lipase, U/L	1742.41(513.00–4630.00)	1895.07(514.72–3357.21)	1642.07(499.00–5052.13)	0.377

Note: P<0.05 is highlighted in bold.
Abbreviations: AP, acute pancreatitis; BMI, body mass index; CNY, Chinese Yuan; CRP, C-reactive protein; CsCa, corrected serum calcium; LOS, length of stay.

Multivariate Analysis of the Short-Term Prognosis of Patients with Malnutrition Diagnosed by GLIM

Since NRS2002 was the first step of GLIM, low BMI, reduced intake, and weight loss were part of both NRS2002 and GLIM, age was part of NRS2002, and low PMA was part of GLIM, we did not treat them as confounding variables to prevent incorporation bias. Although BMI<18.5kg/m^2 was excluded as a confounding variable, overweight/obesity was included as one of the confounding variables. In addition, we adjusted for sex, comorbidity scores, CsCa, and etiology in multivariate logistics regression. Five patients had missing CsCa, so we removed the data from these patients. CsCa was grouped according to our hospital's lower limit of normal values.

Multivariate logistic regression showed malnutrition was significantly associated with local complications (OR 3.42, 95% CI: 1.37–8.50) after adjusting for confounders (Table 5). We found an interaction between malnutrition and overweight/obesity on local complications (p for interaction = 0.023). The rate of local complications in the

Table 2 The Baseline Characteristics, Clinical Outcomes, and Hematologic Parameters of All AP Patients and Malnourished AP Patients Identified by Global Leadership Initiative on Malnutrition Criteria (Grouped by Age)

	<70 years				≥70 years			
	Total (n = 231)	**Malnourished (n = 25)**	**Well-Nourished (n = 206)**	**p**	**Total (n = 38)**	**Malnourished (n = 13)**	**Well-Nourished (n = 25)**	**p**
Female, n(%)	88(38.1)	12(48.0)	76(36.9)	0.285	23(60.5)	7(53.8)	16(64.0)	0.728
Age, years	46(36–56)	52(37–60)	46(37–54)	0.159	78.0(72.0–82.0)	82.5(73.0–88.0)	76(72.0–79.0)	**0.043**
AP history, n(%)	68(29.4)	11(44.0)	57(27.7)	0.106	8(21.1)	4(30.8)	4(16.0)	0.407
Overweight/obesity, n(%)	162(70.1)	8(32.0)	154(74.8)	**<0.001**	17(44.7)	1(7.7)	16(64.0)	**0.001**
BMI, kg/m^2	25.76(23.44–28.09)	22.04(18.37–26.01)	26.08(23.91–28.61)	**<0.001**	23.56(20.00–26.65)	18.84(17.05–20.26)	25.32(23.41–27.43)	**<0.001**
Comorbidity score	0(0–0)	0(0–0)	0(0–0)	0.580	0(0–2)	0(0–2)	0(0–1)	0.581
Aetiology, n(%)				0.965				0.549
Biliary	48(20.8)	5(20.0)	43(20.9)		21(55.3)	9(69.2)	12(48.0)	
Hypertriglyceridemic	47(20.3)	4(16.0)	43(20.9)		0	0	0	
Alcoholic	77(33.3)	9(36.0)	68(33.0)		1(2.6)	0(0)	1(4.0)	
Other	59(25.5)	7(28.0)	52(25.2)		16(42.1)	4(30.8)	12(48.0)	
AP classification, n(%)				0.070				0.638
Mild	162(70.1)	13(52.0)	149(72.3)		28(73.7)	11(84.6)	17(68.0)	
Moderately severe	49(21.2)	8(32.0)	41(19.9)		6(15.8)	1(7.7)	5(20.0)	
Severe	20(8.7)	4(16.0)	16(7.8)		4(10.5)	1(7.7)	3(12.0)	
LOS, days	9(7.0–12.0)	13(7.5–16.0)	9(7.0–11.0)	**0.034**	9.5(6.0–14.0)	7.0(3.5–11.0)	10.0(7.5–14.0)	0.050
Hospitalization costs, CNY	9166.30(6359.97–14,358.33)	13,655.16(10,040.70–23,292.22)	8707.16(6293.59–13,976.51)	**0.002**	10,000.33(7144.12–20,086.97)	10,051.62(6561.16–15,597.16)	9949.03(7300.64–21,590.22)	0.489
Infectious complications, n(%)	16(6.9)	5(20.0)	11(5.3)	**0.019**	2(5.3)	0(0)	2(8.0)	0.538
Local complications, n(%)	43(18.6)	12(48.0)	31(15.0)	**<0.001**	4(10.5)	1(7.7)	3(12.0)	1
Organ failure, n(%)	38(16.5)	7(28.0)	31(15.0)	0.147	7(18.4)	1(7.7)	6(24.0)	0.385
Systemic complications, n(%)	21(9.1)	4(16.0)	17(8.3)	0.258	4(10.5)	1(7.7)	3(12.0)	1
Composite adverse outcome, n(%)	68(29.4)	12(48.0)	56(27.2)	**0.038**	10(26.3)	2(15.4)	8(32.0)	0.441
CRP, mg/L	74.14(14.49–144.16)	101.14(7.72–170.27)	69.75(14.19–139.85)	0.387	18.30(1.18–90.87)	4.33(0.50–63.38)	35.88(12.50–105.21)	0.226
Hemoglobin, g/L	153.00(137.00–166.00)	140.00(118.50–158.00)	154.00(138.50–167.00)	**0.001**	136.00(121.25–154.00)	137.00(117.75–151.25)	138.00(122.75–154.75)	0.817
Neutrophil count, $\times 10^9/L$	10.07(7.11–12.91)	8.59(5.52–10.89)	10.13(7.25–13.32)	0.051	7.90(6.04–10.46)	6.40(5.40–7.42)	10.34(7.11–11.97)	**0.005**
Lymphocyte count, $\times 10^9/L$	1.29(0.86–1.91)	1.02(0.85–1.29)	1.33(0.86–1.95)	**0.040**	0.79(0.59–1.28)	0.97(0.63–1.75)	0.66(0.42–1.18)	0.181
Albumin, g/L	42.37(37.70–45.01)	37.10(32.61–44.50)	42.57(37.93–45.12)	**0.002**	39.63(36.38–43.07)	39.52(36.76–44.38)	39.96(34.18–42.87)	0.770
Blood glucose, mmol/L	8.06(6.63–11.55)	7.49(5.99–11.62)	8.14(6.71–11.58)	0.695	7.77(5.99–9.09)	6.53(5.30–8.51)	8.12(6.74–9.53)	0.092
Total cholesterol, mmol/L	5.04(3.96–6.75)	4.44(3.44–6.18)	5.15(4.06–6.88)	0.050	4.30(3.23–4.79)	4.35(2.93–4.61)	4.30(3.33–4.83)	0.603
Triglycerides, mmol/L	3.37(1.46–9.13)	1.84(1.14–4.87)	3.69(1.49–9.77)	0.097	1.11(0.90–1.59)	0.94(0.65–1.07)	1.32(1.02–1.95)	**0.002**
CsCa, mmol/L	2.19(2.10–2.24)	2.21(2.02–2.24)	2.18(2.10–2.24)	0.691	2.22(2.16–2.29)	2.23(2.18–2.27)	2.20(2.15–2.31)	0.770
Creatinine, μmol/L	59.20(47.60–74.90)	60.90(49.15–103.05)	58.10(47.50–74.25)	0.208	68.90(53.88–93.05)	60.90(54.73–74.53)	76.35(53.65–120.05)	0.094
Urea nitrogen, mmol/L	4.77(3.89–6.20)	5.03(3.01–9.71)	4.68(3.97–5.91)	0.299	6.29(5.28–7.91)	5.91(4.92–7.56)	6.73(5.39–9.46)	0.110
Amylase, U/L	297.90(125.50–737.10)	342.10(151.75–535.65)	290.60(120.15–765.25)	0.948	849.30(400.25–1880.23)	704.40(366.75–1324.85)	1350.65(682.63–2080.23)	0.224
Lipase, U/L	1493.81(496.00–4206.39)	1493.81(514.72–2439.84)	1427.17(456.75–4667.15)	0.252	3867.81(1835.53–5776.90)	3652.36(717.84–5417.50)	4646.78(2476.76–6574.31)	0.202

Note: P<0.05 is highlighted in bold.

Abbreviations: AP, acute pancreatitis; BMI, body mass index; CNY, Chinese Yuan; CRP, C-reactive protein; CsCa, corrected serum calcium; LOS, length of stay.

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Table 3 The Baseline Characteristics, Clinical Outcomes, and Hematologic Parameters of All AP Patients and Malnourished AP Patients Identified by Global Leadership Initiative on Malnutrition Criteria (Grouped by Overweight/Obesity)

	Non-Overweight/Obesity				Overweight/obesity			
	Total (n = 90)	**Malnourished (n = 29)**	**Well-Nourished (n = 61)**	**p**	**Total (n = 179)**	**Malnourished (n = 9)**	**Well-Nourished (n = 170)**	**p**
Female, n(%)	43(47.8)	13(44.8)	30(49.2)	0.822	68(38.0)	6(66.7)	62(36.5)	0.085
Age, years	59(47.0–67.0)	66(47.5–81.5)	56(48.0–66.0)	**0.036**	45(36.0–55.0)	55(43.5–60.0)	45(36.0–54.0)	0.199
AP history, n(%)	23(25.6)	13(44.8)	10(16.4)	**0.008**	53(29.6)	2(22.2)	51(30.0)	1
BMI, kg/m^2	21.97(19.92–23.15)	18.38(17.47–20.19)	22.38(21.47–23.44)	**<0.001**	27.22(25.56–29.30)	27.01(25.86–29.54)	27.34(25.49–29.30)	0.690
Comorbidity score	0(0–1)	0(0–0)	0(0–1)	0.879	0(0–0)	0(0–0)	0(0–0)	0.957
Aetiology, n(%)				0.684				0.159
Biliary	30(33.3)	11(37.9)	19(31.1)		39(21.8)	3(33.3)	36(21.2)	
Hypertriglyceridemic	8(8.9)	1(3.4)	7(11.5)		39(21.8)	3(33.3)	36(21.2)	
Alcoholic	27(30.0)	9(31.0)	18(29.5)		51(28.5)	0(0)	51(30.0)	
Other	25(27.8)	8(27.6)	17(27.9)		50(27.9)	3(33.3)	47(27.6)	
AP classification, n(%)				0.750				**0.026**
Mild	65(72.2)	21(72.4)	44(72.1)		125(69.8)	3(33.3)	122(71.8)	
Moderately severe	18(20.0)	5(17.2)	13(21.3)		37(20.7)	4(44.4)	33(19.4)	
Severe	7(7.8)	3(10.3)	4(6.6)		17(9.5)	2(22.2)	15(8.8)	
LOS, days	9(7.0–13.0)	9(5.0–14.0)	10(7.5–13.0)	0.341	9(6.0–12.0)	15(8.0–16.0)	9(6.0–12.0)	**0.039**
Hospitalization costs, CNY	10729.53(7117.26–20,770.08)	10,910.59(7219.98–23,292.22)	10,547.12(7066.48–20,243.70)	0.675	8584.06(6314.87–13,916.47)	13,644.91(11,319.34–14,358.33)	8356.96(6223.01–13,137.72)	**0.008**
Infectious complications, n(%)	7(7.8)	2(6.9)	5(8.2)	1	11(6.1)	3(33.3)	8(4.7)	**0.012**
Local complications, n(%)	18(20.0)	7(24.1)	11(18.0)	0.576	29(16.2)	6(66.7)	23(13.5)	**0.001**
Organ failure, n(%)	13(14.4)	5(17.2)	8(13.1)	0.749	32(17.9)	3(33.3)	29(17.1)	0.203
Systemic complications, n(%)	8(8.9)	3(10.3)	5(8.2)	0.709	17(9.5)	2(22.2)	15(8.8)	0.206
Composite adverse outcome, n(%)	25(27.8)	8(27.6)	17(27.9)	1	53(29.6)	6(66.7)	47(27.6)	**0.021**
CRP, mg/L	31.68(2.21–101.48)	15.42(0.91–141.77)	38.09(3.06–98.17)	0.886	88.11(20.07–149.80)	131.69(18.61–208.94)	81.21(16.97–149.33)	0.205
Hemoglobin, g/L	140.0(125.0–155.0)	140.0(124.0–158.0)	143.0(127.0–156.0)	0.488	156.0(139.0–168.0)	126.5(93.3–151.8)	156.5(140.0–170.0)	**0.002**
Neutrophil count, $\times 10^9/L$	8.11(5.91–10.78)	6.96(6.10–9.28)	9.47(5.80–11.37)	**0.045**	10.50(7.28–13.35)	7.07(5.07–15.88)	10.55(7.52–13.38)	0.108
Lymphocyte count, $\times 10^9/L$	1.02(0.70–1.34)	0.97(0.74–1.24)	1.01(0.66–1.38)	0.912	1.48(0.86–2.06)	1.2(0.83–2.35)	1.47(0.84–2.06)	0.464
Albumin, g/L	40.17(36.94–44.14)	39.58(36.37–44.35)	40.91(37.71–44.50)	0.211	42.91(37.63–45.01)	34.53(30.20–42.70)	42.69(37.72–45.02)	**0.010**
Blood glucose, mmol/L	7.52(6.07–10.46)	7.30(5.65–9.83)	7.78(6.25–10.70)	0.286	8.28(6.72–11.29)	8.00(5.43–11.14)	8.37(6.86–11.40)	0.946
Total cholesterol, mmol/L	4.24(3.54–5.44)	4.44(3.01–4.91)	4.23(3.54–5.66)	0.254	5.13(4.11–6.90)	4.53(3.36–5.93)	5.22(4.20–7.12)	0.346
Triglycerides, mmol/L	1.35(0.86–3.68)	1.09(0.92–1.67)	1.59(0.84–3.78)	0.191	3.58(1.62–10.10)	1.88(1.52–9.63)	4.08(1.62–10.52)	0.505
CsCa, mmol/L	2.21(2.13–2.26)	2.22(2.17–2.24)	2.19(2.12–2.25)	0.247	2.18(2.09–2.24)	2.17(2.04–2.26)	2.18(2.09–2.24)	0.341
Creatinine, μmol/L	58.45(46.88–75.98)	60.90(53.15–80.40)	56.70(46.40–74.50)	0.296	60.70(49.50–76.40)	61.80(41.58–89.75)	60.25(48.70–75.73)	0.528
Urea nitrogen, mmol/L	5.69(4.33–7.41)	6.12(4.22–8.66)	5.49(4.31–6.98)	0.455	4.68(3.94–6.08)	3.33(2.82–9.23)	4.68(3.99–5.92)	0.690
Amylase, U/L	471.00(196.23–1303.68)	476.00(342.00–917.30)	466.00(158.10–1314.20)	0.772	291.30(113.35–742.40)	201.65(103.80–522.03)	309.65(112.28–782.18)	0.421
Lipase, U/L	1878.33(730.60–5402.45)	2000.00(906.64–4252.18)	1831.00(639.56–5970.66)	0.296	1450.77(440.49–4490.87)	522.55(115.82–2281.85)	1524.12(436.56–4695.34)	0.093

Note: P<0.05 is highlighted in bold.

Abbreviations: AP, acute pancreatitis; BMI, body mass index; CNY, Chinese Yuan; CRP, C-reactive protein; CsCa, corrected serum calcium; LOS, length of stay.

Table 4 Prevalence of Malnutrition and κ of Each GLIM Combination in Patients with Acute Pancreatitis Overall and in Various Subgroups, Considering GLIM Criteria (Any Phenotypic Criteria + Any Etiologic Criteria) as the Reference Method

Combination		Total		Non-overWeight/obesity		OverWeight/obesity		<70 years		≥70 years		MAP		MSAP+SAP	
		N (%)	κ	N	κ	N	κ	N	κ	N	κ	N	κ	N	κ
	1 phenotypic and 1 etiologic criteria														
GLIM1	Weight loss + ↓Food intake	6(2.2)	0.24	3	0.14	3	0.49	4	0.25	2	0.19	3	0.20	3	0.31
GLIM2	Weight loss + Inflammation	9(3.3)	0.35	6	0.26	3	0.49	7	0.41	2	0.19	5	0.32	4	0.40
GLIM3	Low BMI + ↓Food intake	5(1.8)	0.21	5	0.22	0	–	2	0.13	3	0.28	4	0.26	1	0.11
GLIM4	Low BMI + Inflammation	19(7.0)	0.63	19	0.72	0	–	10	0.54	9	0.75	16	0.78	3	0.31
GLIM5	↓Muscle mass + ↓Food intake	9(3.3)	0.35	4	0.18	5	0.70	8	0.46	1	0.10	3	0.20	6	0.55
GLIM6	↓Muscle mass + Inflammation	31(11.5)	0.62	21	0.45	10	0.83	25	0.64	6	0.53	13	0.44	18	0.84
	1 phenotypic and 2 etiologic criteria														
GLIM7	Weight loss + ↓Food intake + Inflammation	6(2.2)	0.24	3	0.14	3	0.49	4	0.25	2	0.19	3	0.20	3	0.31
GLIM8	Low BMI + ↓Food intake + Inflammation	5(1.8)	0.21	5	0.22	0	–	2	0.13	3	0.28	4	0.26	1	0.11
GLIM9	↓Muscle mass + ↓Food intake + Inflammation	9(3.3)	0.35	4	0.18	5	0.70	8	0.46	1	0.10	3	0.20	6	0.55
	2 phenotypic and 1 etiologic criteria														
GLIM10	Weight loss + Low BMI + ↓Food intake	1(0.3)	0.04	1	0.05	0	–	0	–	1	0.10	1	0.07	0	–
GLIM11	Weight loss + Low BMI + Inflammation	1(0.3)	0.04	1	0.05	0	–	0	–	1	0.10	1	0.07	0	–
GLIM12	Weight loss + ↓Muscle mass + ↓Food intake	3(1.1)	0.13	1	0.05	2	0.35	3	0.20	0	–	0	–	3	0.31
GLIM13	Weight loss + ↓Muscle mass + Inflammation	4(1.4)	0.17	2	0.09	2	0.35	4	0.25	0	–	0	–	4	0.40
GLIM14	Low BMI + ↓Muscle mass + ↓Food intake	2(0.7)	0.09	2	0.09	0	–	2	0.13	0	–	1	0.07	1	0.11
GLIM15	Low BMI + ↓Muscle mass + Inflammation	8(2.9)	0.31	8	0.34	0	–	5	0.31	3	0.28	5	0.32	3	0.31
	2 phenotypic and 2 etiologic criteria														
GLIM16	Weight loss + Low BMI + ↓Food intake + Inflammation	1(0.3)	0.04	1	0.05	0	–	0	–	1	0.10	1	0.07	0	–
GLIM17	Low BMI + ↓Muscle mass + ↓Food intake + Inflammation	2(0.7)	0.09	2	0.09	0	–	2	0.13	0	–	1	0.07	1	0.11
GLIM18	Weight loss + ↓Muscle mass + ↓Food intake + Inflammation	3(1.1)	0.13	1	0.05	2	0.35	3	0.20	0	–	0	–	3	0.31
	3 phenotypic and 1 etiologic criteria														
GLIM19	Weight loss + Low BMI + ↓Muscle mass + ↓Food intake	0	–	0	–	0	–	0	–	0	–	0	–	0	–
GLIM20	Weight loss + Low BMI + ↓Muscle mass + Inflammation	0	–	0	–	0	–	0	–	0	–	0	–	0	–
	3 phenotypic and 2 etiologic criteria														
GLIM21	Weight loss + Low BMI + ↓Muscle mass + ↓Food intake + Inflammation	0	–	0	–	0	–	0	–	0	–	0	–	0	–

Note: ↓ reduced.

Abbreviations: BMI, body mass index; GLIM, Global Leadership Initiative on Malnutrition; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis.

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Table 5 Association Between Malnutrition and Various Clinical Outcomes in Patients with Acute Pancreatitis

Outcome	Model 1	Model 2
	OR (95% CI)	OR (95% CI)
Infectious complications	NS	NS
Local complications	2.92 (1.34–6.35)	3.42 (1.37–8.50)
Organ failure	NS	NS
Systemic complications	NS	NS
Composite adverse outcome	NS	NS

Notes: Model 1: adjusted for sex. Model 2: adjusted for sex, comorbidity score, overweight/obesity, corrected serum calcium, and aetiology.
Abbreviations: CI, confidence intervals; NS, no significance; OR, odds ratio.

overweight/obesity subgroup was 12.2 times higher (95% CI: 2.51–59.37) in malnourished patients than in well-nourished patients. Still, there was no difference in the rate of local complications between malnourished and well-nourished patients in the non-overweight/obesity subgroup (Table 6). Therefore, we performed a subgroup analysis of the overweight/obesity subgroup. Multivariate logistic regression also showed malnutrition was significantly associated with infectious complications (OR 9.95, 95% CI: 1.25–79.44) and composite adverse outcome (OR 4.78, 95% CI: 1.05–21.73) after adjusting for confounders (Table 7).

Since we did not include age as a confounding variable and there were differences in several clinical outcomes between the malnourished and well-nourished groups among patients <70 years in the previous univariate analyses, we conducted the analyses separately among patients <70 years. Multivariate logistic regression showed malnutrition was significantly associated with infectious complications (OR 5.31, 95% CI: 1.27–22.14), local complications (OR 5.63, 95% CI: 2.05–15.43) and composite adverse outcome (OR 2.79, 95% CI: 1.06–7.35) after adjusting for confounders (Table 8).

We also performed a subgroup analysis in patients <70 years, and there was an interaction between overweight/obesity still and malnutrition on infectious complications, local complications, and composite adverse outcome. Additionally, we found an interaction between sex and malnutrition on the composite adverse outcome (p for interaction 0.061), with female

Table 6 Stratified Associations Between Malnutrition and Local Complications

	Well–Nourished	Malnourished	p	p for Interaction
Aetiology	–	–	–	0.415
Biliary	–	–	–	
Hypertriglyceridemic	–	–	–	
Alcoholic	–	–	–	
Other	–	–	–	
Sex	–	–	–	0.499
Men	–	–	–	
Women	–	–	–	
Comorbidity score	–	–	–	0.639
0	–	–	–	
≥ 1	–	–	–	
CsCa, mmol/L	–	–	–	0.117
< 2.11	–	–	–	
≥ 2.11	–	–	–	
Overweight/obesity	–	–	–	**0.023**
Yes	1 (ref)	12.20 (2.51–59.37)	**0.002**	
No	1 (ref)	2.04 (0.61–6.88)	0.251	

Notes: Analyses were adjusted for aetiology, sex, overweight/obesity, comorbidity score, and CsCa when they were not the strata variables. P<0.05 is highlighted in bold.
Abbreviation: CsCa, corrected serum calcium.

Table 7 Association Between Malnutrition and Various Clinical Outcomes in Overweight/Obesity Patients with Acute Pancreatitis

Outcome	Model 1	Model 2
	OR (95% CI)	OR (95% CI)
Infectious complications	8.79 (1.79–43.17)	9.95 (1.25–79.44)
Local complications	10.82 (2.48–47.25)	12.20 (2.51–59.37)
Organ failure	NS	NS
Systemic complications	NS	NS
Composite adverse outcome	5.17 (1.22–21.84)	4.78 (1.05–21.73)

Notes: Model 1: adjusted for sex. Model 2: adjusted for sex, comorbidity score, corrected serum calcium, and aetiology.
Abbreviations: CI, confidence intervals; NS, no significance; OR, odds ratio.

Table 8 Association Between Malnutrition and Various Clinical Outcomes in Patients with Acute Pancreatitis<70 Years

Outcome	Model 1	Model 2
	OR (95% CI)	OR (95% CI)
Infectious complications	4.28 (1.35–13.64)	5.31 (1.27–22.14)
Local complications	4.93 (2.02–12.01)	5.63 (2.05–15.43)
Organ failure	NS	NS
Systemic complications	NS	NS
Composite adverse outcome	2.40 (1.03–5.59)	2.79 (1.06–7.35)

Notes: Model 1: adjusted for sex. Model 2: adjusted for sex, comorbidity score, overweight/obesity, corrected serum calcium, and aetiology.
Abbreviations: CI, confidence intervals; NS, no significance; OR, odds ratio.

malnourished patients being 6.75 times (95% CI 1.49–30.68) more likely to have composite adverse outcome than well-nourished patients, whereas malnutrition and composite adverse outcome were not associated in male patients (Table 9).

Discussion

The GLIM working group recommended that the validation of the GLIM criteria consist of comparing the "gold standard" and the ability to predict a future outcome.[12] The working group also recommended that both sensitivity and specificity should be>80% when conducting criteria validity.[12] Subjective global assessment (SGA) has been used as the gold standard or semi-gold standard for malnutrition, and patient-generated subjective global assessment (PG-SGA) has been used as the gold standard or semi-gold standard for malnutrition in oncology patients. Our hospital did not routinely perform SGA at the time of patient hospitalization, therefore, we did not validate the agreement between GLIM and SGA.

Some studies have reported that the sensitivity and specificity of GLIM can reach 80%, as required by the GLIM working group. A systematic review and meta-analysis showed the estimated results from all 20 studies: The pooled sensitivity was 0.72 (95% CI, 0.64–0.78), and specificity was 0.82 (95% CI, 0.72–0.88). The reference standards for these studies were not all SGA or PG-SGA. According to the subgroup analysis, when SGA was used as the reference standard, the GLIM criteria seemed to have a better diagnostic value (sensitivity, 0.81; specificity, 0.80).[13] The Bayesian latent class model (BLCM) can be used to evaluate diagnostic performance without a "gold standard". Nakyeyune et al reported that the sensitivity and specificity of the GLIM criteria were 0.85 and 0.88 respectively by applying BLCM, but both were lower than that of PG-SGA in patients with lung cancer.[14]

AP patients are prone to malnutrition, which is associated with reduced feeding, increased energy requirements, and protein catabolism. Combined malnutrition in AP patients is associated with higher mortality, sepsis, severe sepsis, infectious shock, respiratory failure, longer hospital stays, and higher hospitalization costs.[15,16] The definition of

Table 9 Stratified Associations Between Malnutrition and Infectious Complications, Local Complications, and Composite Adverse Outcome in Patients with Acute Pancreatitis <70 Years

	Infectious Complications				Local Complications				Composite Adverse Outcome			
	Well-Nourished	Malnourished	p	p for Interaction	Well-Nourished	Malnourished	p	p for Interaction	Well-Nourished	Malnourished	p	p for Interaction
Aetiology	–	–	–	0.569	–	–	–	0.149	–	–	–	0.135
Biliary	–	–	–		–	–	–		–	–	–	
Hypertriglyceridemic	–	–	–		–	–	–		–	–	–	
Alcoholic	–	–	–		–	–	–		–	–	–	
Other	–	–	–		–	–	–		–	–	–	
Sex				0.582	–	–	–	0.382	–	–	–	0.061
Men	–	–	–		–	–	–		1 (ref)	1.01 (0.24–4.34)	0.989	
Women	–	–	–		–	–	–		1 (ref)	6.75 (1.49–30.68)	**0.013**	
Comorbidity score				0.987	–	–	–	0.999	–	–	–	0.999
0	–	–	–		–	–	–		–	–	–	
≥ 1	–	–	–		–	–	–		–	–	–	
CsCa, mmol/L				0.164	–	–	–	0.555	–	–	–	0.708
< 2.11	–	–	–		–	–	–		–	–	–	
≥ 2.11	–	–	–		–	–	–		–	–	–	
Overweight/obesity				0.099	–	–	–	0.071	–	–	–	0.083
Yes	1 (ref)	13.04 (1.52–111.80)	**0.019**		1 (ref)	17.92 (2.96–108.54)	**0.002**		1 (ref)	8.07 (1.40–46.68)	**0.020**	
No	1 (ref)	3.40 (0.38–30.36)	0.273		1 (ref)	4.00 (0.94–17.06)	0.061		1 (ref)	2.15 (0.55–8.37)	0.270	

Notes: Analyses were adjusted for aetiology, sex, overweight/obesity, comorbidity score, and CsCa when they were not the strata variables. P<0.05 is highlighted in bold.
Abbreviation: CsCa, corrected serum calcium.

malnutrition in previous studies lacked uniform standards. Our study was the first to validate the GLIM criteria in AP and confirm the impact of malnutrition on the prognosis of AP. In addition, we also found an increased incidence of local complications in malnourished AP patients than well-nourished AP patients and that malnutrition was an independent risk factor for local complications. Malnutrition and overweight/obesity interacted on multiple adverse outcomes, and malnutrition was associated with various adverse outcomes only in the overweight/obesity subgroups. We also found that LOS was longer and that malnutrition was also associated with multiple adverse outcomes in malnourished patients in the <70 years subgroup. Regarding the presence of age subgroup differences, we believed that this may be because four of the 13 malnourished patients in the ≥70 years group were discharged against medical advice (DAMA) (eg an 83-year-old male SAP patient was discharged after only two days of hospitalization) in a higher proportion than in all the other groups, which resulted in a shorter LOS and a decrease in the number of cases with poor prognosis. Therefore, we speculated that the difference in age subgroups did not exist but that the DAMA in the ≥70 years subgroup masked differences in infectious complications and composite adverse outcome that should have existed in the overall patient population. Regarding the existence of differences in aetiologic subgroups, we considered that it was because there was no difference in overweight/obesity rates between malnourished and well-nourished patients only in the hypertriglyceridemic subgroup. This means that only in the hypertriglyceridemic subgroup were overweight/obesity rates higher rather than lower in malnourished patients. This confirms the previous results in the overweight/obese subgroup that malnutrition is associated with various adverse outcomes only in overweight/obese patients.

As a diagnostic standard for malnutrition, GLIM criteria were not a tool that primarily intended to predict outcomes such as mortality or complications. But indeed, malnutrition was one of the important factors that affected outcomes. There have been many studies of the predictive utility of GLIM in other diseases, with most studies conducted in cancer patients. The GLIM criteria were effective in predicting mortality or survival in cancer patients, and malnutrition defined by GLIM was associated with an increased risk of complications, longer hospitalization, and poorer quality of life in cancer patients.[17–21] 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 one year.[22] GLIM has also shown good predictive utility in patients with other diseases, such as chronic liver disease[23] and heart failure.[24] In addition, malnutrition defined by GLIM was associated with mortality in both hospitalized elderly patients and the community elderly.[25,26] However, there were different conclusions regarding the predictive role of GLIM. For example, Okada et al found that malnutrition diagnosed by GLIM was not a poor prognostic factor for overall survival (OS) in patients with esophageal cancer.[27] In the studies of intensive care unit patients, the prediction of LOS and mortality risk by GLIM was controversial.[28,29]

Overweight/obesity is one of the poor prognostic factors for AP. AP patients with a BMI >25 kg/m^2 had an almost three-fold increased risk for SAP compared to normal BMI (OR = 2.87, 95% CI: 1.90–4.35). A BMI >30 kg/m^2 resulted in a three times higher risk of mortality compared to a BMI <30 kg/m^2 (OR=2.89, 95% CI:1.10–7.36).[30] Obesity was also independently associated with the development of organ failure (relative risk (RR)= 1.38, 95% CI: 1.11–1.73) and multiple organ failure (RR= 1.81, 95% CI: 1.35–2.42).[31] Obesity worsens AP severity by allowing unregulated lipolysis of visceral fat enriched in unsaturated triglyceride, thus releasing unsaturated fatty acids which inhibit mitochondrial complexes I and V, cause necrosis.[32] However, there have been no studies simultaneously investigating the relationship between obesity combined with malnutrition and the prognosis of AP. To the best of our knowledge, this is the first study to find an interaction between overweight/obesity and GLIM-defined malnutrition. In our study, we set 24 kg/m^2 and 28 kg/m^2 as the cutoff values for overweight and obesity, respectively, because they are the diagnostic standards in China. Our study showed an association between malnutrition and multiple adverse outcomes only in overweight/obese AP patients. Our study is similar to Chien's in that they observed the highest burden of comorbidities and the most unfavorable cardiac outcomes in obese (>25 kg/m^2)-malnourished (GLIM-defined) patients, higher than lean (≤25 kg/m^2)-malnourished and obese-well-nourished groups.[33] Similarly, Zhou's study found that rectal cancer patients with visceral obesity defined by CT measurement of visceral fat area and malnutrition defined by GLIM were more likely to have postoperative complications, and the OS and cancer-specific survival were poorer.[34] The potential relationship between overweight/obesity and malnutrition should be explored further, and overweight/obese patients in combination with malnutrition deserve focused attention. In addition, we observed an association between malnutrition and composite

adverse outcome in patients <70 years only in female patients. The reason for this is unclear, and it still needs to be validated in large samples.

Limitation

First, since this was a retrospective study from a single institution, and the sample size was relatively small, there might be some bias, especially selection bias. Second, due to our strict two-step screening according to the GLIM criteria, some negative NRS2002 screening patients were not assessed for malnutrition. However, studies showed that the two-step method may miss the diagnosis of some malnourished patients. Thus, a number of cases of patients with malnutrition could have been missed in this study. Third, we did not compare the GLIM criteria to SGA because SGA is not routinely adopted into clinical practice at our hospital, so the validation of our GLIM may be incomplete. In addition, some patients who were DAMA may have contributed to the inaccuracy and poor interpretation of some of the results.

Conclusion

This study was the first to validate the predictive validity of the GLIM criteria in AP patients. Malnourished AP patients were more likely to have multiple adverse outcomes and higher hospitalization costs and LOS than well-nourished patients. However, malnutrition diagnosed by GLIM criteria only predicted poor prognosis in overweight/obese AP patients.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on 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 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. Prior to 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.

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Disclosure

The authors report no conflicts of interest in this work.

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