Original Article

Construction and validation of a predictive model for the risk of three-month-postoperative malnutrition in patients with gastric cancer: a retrospective case-control study

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Background: This study analyzed both the influencing factors of malnutrition in patients with gastric cancer and established a multi-dimensional risk model to predict postoperative malnutrition three months after surgery.

Methods: The clinical data of gastric cancer patients hospitalized for the first time and receiving laparoscopic surgery in the general surgery department of our hospital were retrospectively analyzed through the hospital information system and divided into a training set and a validation set in the ratio of 7:3. Nutritional status was assessed using the Patient Generated Subjective Global Assessment scale and follow-up records three months after surgery. Patients were divided into a non-malnutrition group and a malnutrition group, and a risk prediction model was established and displayed in the form of a nomogram.

Results: A total of 344 patients were included, with 242 in the training and 102 in the validation set. Tumor node metastasis stage (TNM Stage, P=0.020), cardiac function grading (CFG, P=0.013), prealbumin (PAB, P<0.001), neutrophil-to-lymphocyte ratio (NLR, P=0.027), and enteral nutrition within 48 hours post-operation (EN 48 h post-op, P=0.025) were independent risk factors. We established a prediction model with the above variables and displayed it via a nomogram, then verified its effectiveness through internal and external verification. This revealed a C-index of 0.84 (95% CI: 0.79–0.89), and the area under curve (AUC) areas of 0.840 (training set) and 0.854 (validation set), which was better than the nutritional risk screening 2002 (NRS2002) scale. The calibration curve brier scores were 0.159 and 0.195, and the Hosmer-Lemeshow test chi-square values were 14.070 and 1.989 (P>0.05). The decision curve analysis (DCA) of the training set model indicated the clinical applicability was good and within the threshold probability range of 10%–85%, which was also better than NRS2002.

Conclusions: A clinical prediction model including multi-dimensional variables was established based on independent risk factors of malnutrition three months after gastrectomy in patients with gastric cancer. The model yields greater prediction accuracy of the risk of three-month-postoperative malnutrition in patients with gastric cancer, helps screen high-risk patients, formulates targeted nutritional prescriptions early, and improves the overall prognosis of patients.

Keywords: Gastric cancer; post-operation; malnutrition; prediction model

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Introduction

Gastric cancer is more common gastrointestinal tumor. According to global cancer statistics (Globocan 2020), it is the fifth most common cancer and the fourth leading cause of cancer death worldwide (1). Gastric cancer has a considerable influence on the appetite, digestion, and absorption functions of patients and can induce a decrease in nutritional intake. Additionally, the resting energy expenditure (REE) of patients with gastric cancer increases, and both are mutually causal, which increases their energy demands. However, the feedback mechanism between the resting energy expenditure and food intake is destroyed by the decrease in appetite. Consequently, food intake does not increase, resulting in a significant negative energy balance (2). Additionally, factors such as continuous stress, chronic inflammation, and consumptive metabolic disorder can impact the nutritional status of patients (3). Finally, as surgery and chemotherapy are the mainstream treatment methods, surgical resection of part or all of the stomach causes not only trauma to the body but a further decline of gastric function, anorexia, and an aggravation of digestive tract reactions. More than 50% of patients with gastric cancer are in a state of malnutrition after surgery, and their average weight decreases by 10–20% (4). In addition, chemotherapy leads to severe gastrointestinal reactions and immunosuppression, also affecting nutritional status (5,6). From the perspective of pathophysiology, the nutritional status of patients is closely associated with material metabolism, the functional operation of important organs, the immune response, and cell membrane stability. Clinically, postoperative malnutrition induces an increase in the incidence of complications such as infection, impaired wound healing, and anastomotic fistula, which aggravate malnutrition and form a vicious circle. Study has shown the risk of death within five years following gastric cancer surgery for malnourished patients is 83% higher than for those with normal nutritional status (7). Moreover, postoperative malnutrition is positively correlated with the recurrence rate and negatively correlated with the disease-free survival rate and overall survival rate (8). Therefore, malnutrition has a negative impact on postoperative rehabilitation, survival rate and overall prognosis of gastric cancer patients.

Most existing diagnostic criteria show hysteresis for this unfortunate postoperative state. As its cause involves many pathophysiological mechanisms, and a single index cannot fully explain it, early warning and intervention are essential. At present, nutritional risk screening scales, such as the nutritional risk screening 2002 (NRS2002) score, are not designed specifically for gastric cancer patients. Therefore, based on the pathogenesis, using the perioperative-related indicators to establish a multi-dimensional risk prediction model to identify high-risk patients early is a more effective method to prevent postoperative malnutrition. We present the following article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1307/rc).

Highlight box

Key findings
- Establishment and validation of early risk prediction model for postoperative malnutrition of gastric cancer.

What is known and what is new?
- TNM stage, PAB, cardiac function, inflammatory reaction and early enteral nutrition, a single factor, are associated with postoperative malnutrition in gastric cancer.
- During the perioperative period, the above five factors were jointly predicted, and internal and external validation was conducted after modeling.

What is the implication, and what should change now?
- It is necessary to accurately assess the nutritional risk of gastric cancer patients after surgery at the time of admission, and then conduct early intervention.

Methods

Participants

A total of 344 patients who received gastric cancer surgery from January 2019–December 2021 in the General Surgery Department of the Second Hospital of Anhui Medical University were selected as research participants. Inclusion criteria: (I) patients aged 30–90 years; (II) laparoscopic radical gastrectomy was successfully performed, and

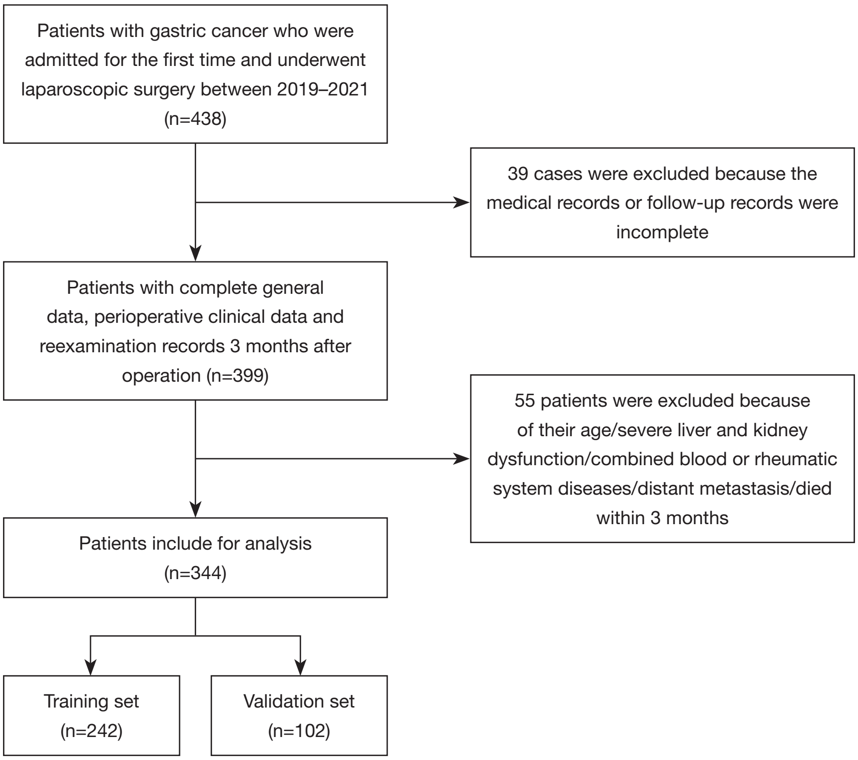

Figure 1 Flow chart of data sources and screening of cases.

postoperative pathology confirmed gastric cancer; (III) the patient's hospitalization and follow-up data for three months after the operation were complete and available for review via the hospital information system (HIS). Exclusion criteria: (I) presence of severe liver and kidney dysfunction; (II) presence of diseases of the blood or rheumatic immune system; (III) patients with distant metastasis (TNM IV phase); (IV) patients who died within three months following surgery. Through screening, 242 cases were finally included in the study (*Figure 1*).

Ethical review

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of the Second Hospital of Anhui Medical University (No. YX-2022-158) and informed consent was taken from all the patients.

Sample size estimation

The effective sample size in predictive studies (modeling and validation) is determined by the number of outcome events. There must be at least 10 positive outcome events per variable to guarantee accuracy and feasibility (9). According to the incidence of malnutrition after gastric cancer surgery reported in a previous study (10), the clinical data of at least 200 patients were required to construct the model. This meant seven or fewer predictors could enter the model in the final multivariate logistic regression model. The sample size of the model established in this study was 242, and the number of positive results was 105, all of which significantly exceeded the events per variable method and could provide a reliable assessment.

Data collection

This was a retrospective case-control study. Candidate variables included general data, perioperative clinical data, and follow-up data pertaining to patients who were hospitalized for gastric cancer in the general surgery department of our hospital from January 2019 to December 2021. In addition, based on the pathogenesis of malnutrition after gastric cancer surgery, relevant literature reports and the consulting results of gastrointestinal surgery and nutrition experts, the risk factor variables were preliminarily selected.

Perioperative data were general data comprising gender, age, body mass index (BMI), and mid-arm muscle circumference (MAMC); history information comprising a history of smoking, alcohol consumption, hypertension, and diabetes mellitus; clinical data (on admission) comprising pain grading, self-care grading, cardiac function grading (CFG), pulmonary function grading, scope of laparoscopic surgery, neoadjuvant, TNM stage of the tumor, degree of differentiation, postoperative chemotherapy, postoperative complications, and enteral nutrition within 48 h post-operation (EN within 48 h post-op); and laboratory results (on admission) comprising hemoglobin, neutrophil-to-lymphocyte ratio (NLR), albumin, prealbumin (PAB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, urea nitrogen, triglycerides, serum sodium, serum potassium, C-reactive protein, carcinoembryonic antigen, and glycosylated hemoglobin.

In addition, patient scores for the NRS2002 on admission were collected. The NRS2002 was published by the European Society of Parenteral and Enteral Nutrition in 2002 (11). It can prospectively and dynamically judge changes in the nutritional status of patients, presents good validity and reliability, and as a classic tool to judge nutritional risk, is widely used in clinical tumor patients. The scale comprises three parts: Scores for the impact of disease on nutritional status, impaired nutritional status, and age, and the total score is the sum of the three items. A score greater than or equal to three indicates malnutrition risk, while a score less than three indicates no malnutrition risk.

Follow-up data included the nutritional status of patients three months after surgery. The evaluation tools used included the Patient Generated Subjective Global Assessment (PG-SGA) scale, which is recommended by the American Dietetic Association for the assessment of nutritional status in oncology patients (12). For this scale, a score greater than or equal to four points is classified as malnutrition, and one less than four points is classified as non-malnutrition. Patients were divided into two groups according to this standard. The nutritional status of patients was assessed after surgery based on the peak period of malnutrition at three months after gastric cancer (13,14). Moreover, patients needed to be routinely reviewed and could be easily evaluated during this time.

Definition and classification standard of relevant indicators

First, a history of hypertension was determined according to the diagnosis certificate of second-level or higher hospitals or by meeting the relevant standards of the "2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (Eighth Joint National Committee)." Second, a history of diabetes was determined following the diagnosis certificate of secondary or higher hospitals or by meeting the relevant standards of "Standards of Medical Care in Diabetes-2020" issued by the American Diabetes Association. Third, a history of smoking was determined based on the average daily smoking being greater than or equal to one cigarette for at least one year. Fourth, a history of alcohol consumption was determined based on the average ethanol intake being more than 40 g/day for at least five years. Fifth, the scope of laparoscopic radical gastrectomy was divided into laparoscopic total gastrectomy (LTG), laparoscopic proximal gastrectomy (LPG), and laparoscopic distal gastrectomy (LDG). Sixth, methods of laparoscopic radical gastrectomy were divided into laparoscopic assisted radical gastrectomy (LAG) and total laparoscopic radical gastrectomy (TLG). Seventh, regarding postoperative complications, according to the guidelines of the International Gastric Cancer Society (IGCC), the statistics included general postoperative complications (14 types) and postoperative surgical complications (10 types) (15).

Classification standard of relevant indicators

First, BMI was divided into the following four grades: <18 kg/m^2, 18–24 kg/m^2, 24–27.5 kg/m^2, and >27.5 kg/m^2. Second, MAMC for men was divided into <25.3 cm and ≥25.3 cm, and for women into <23.2 cm and ≥23.2 cm. Third, pain classification on admission was divided into four grades (no pain, mild pain, moderate pain, and severe pain) according to World Health Organization standards. Fourth, grade of self-care ability on admission was categorized into five grades following the Barthel index: Independent (100 points), mild dependence (91–99 points), moderate dependence (61–90 points), severe dependence (21–60 points), and complete dependence (0–20 points). Fifth, cardiac function grading (CFG) was classified into normal (LVEF >40%, with no diastolic dysfunction), diastolic heart failure (DHF: LVEF >40%, with diastolic dysfunction), and systolic heart failure (SHF: LVEF ≤40%) according to color doppler ultrasound. Sixth, pulmonary function classification was divided into four grades considering the percentage of residual gas volume and total lung volume: More than 80% (normal), 65–79% (slight reduction), 50–64% (moderate reduction), and 35–49% (severe reduction). Seventh, TNM staging of gastric cancer was determined based on the TNM staging standard of the Union for International Cancer Control/American Joint Committee on Cancer Staging in 2010. Eighth, EN within 48 h post-op was divided into yes or no, with enteral nutrition including nasal or oral feeding. Ninth, the degree of differentiation was divided into three grades based on the postoperative pathological results: Well, moderately, and poorly differentiated. Finally, the neoadjuvant status was divided into yes or no, and adjuvant chemotherapy was divided into three grades: No chemotherapy, incomplete chemotherapy, and complete chemotherapy. Both neoadjuvant and adjuvant chemotherapy used the SOX scheme.

Process and statistical methods for model construction and verification

(I) The population was randomly split into a training set and a validation set in a 7:3 ratio using the simple random sampling method (16,17). (II) The training set was used to build the model. (III) The comparability of the training set and verification set data was tested. (IV) The training set and verification set data were used for internal and external verification of the model.

Data description and analysis were conducted using SPSS25.0 software. If the measurement data exhibited a normal distribution, they were expressed as $\bar{x}$±s, and the comparison between groups was performed by *t*-test. If the measurement data presented a non-normal distribution, the median [M (P25, P75)] was adopted, and the Mann-Whitney U test was conducted for comparison between groups. Count or categorical data were expressed as n (%), and comparisons between groups were performed with the chi-square test or Fisher's exact test.

Model establishment: The nutritional status of patients three months after surgery was considered the dependent variable (non-malnutrition or malnutrition). Variables with a statistical difference according to a difference test (P<0.05) combined with those considered significant for patient outcome by clinical professionals were included in multivariate logistic regression. Dummy variables (DV) were set before inclusion for the anisotropism of ordered categorical variables. Stepwise regression was used as follows: the selection was forwarded to the screen, and variables were identified for building the model. Moreover, P value and OR value were used to judge the influence of each factor on the outcome. Finally, the "rms" package of R language (R3.6.1) software was used to draw the nomogram.

Internal and external verification: The receiver operating characteristic (ROC) curve of the model was depicted using the "pROC" package in R language (R3.6.1) software, and the area under curve (AUC) of the training and validation sets was calculated and compared with the prediction performance of the NRS2002 scale to test the discrimination of the model. The "rms" package was adopted to draw the calibration curves of the training set and verification set, respectively, and visual observation and the Hosmer-Lemeshow test were used to evaluate model calibration. Clinical suitability was evaluated by plotting the clinical decision curve using the "rmda" package model. Internal verification was realized by bootstrap self-sampling 1000 times, and P<0.05 was taken to indicate statistically significant differences.

Results

Description of general data and difference test

In the training set, 242 patients were divided into a non-malnutrition group (137 cases, 56.6%) and a malnutrition group (105 cases, 43.4%). The differences in general and clinical data between the two groups were tested, and the results demonstrated statistical differences (P<0.05) in age, TNM stage, cardiac function grading (CFG), carcinoembryonic antigen (CEA), albumin, PAB, hemoglobin, NLR, and triglycerides, as shown in *Table 1*.

Logistic regression analysis of risk factors for postoperative malnutrition in patients with gastric cancer

Variables showing a statistical difference in the difference test (the TNM stage and CFG set dummy variables, TNM I stage, and CFG, with normal as reference) and the variables clinically considered to have an impact on the outcome (neoadjuvant, scope of laparoscopic surgery, adjuvant chemotherapy, enteral nutrition within 48 hours post-operation, and postoperative complications) were included in the logistic regression analysis. The results suggested the TNM stage and CFG were independent risk factors of malnutrition. With TNM I as a reference, the risk of malnutrition in TNM III patients increased by 3.0 times (OR =4.002, 95% CI: 1.670–9.589), and regarding normal CFG, the risk of malnutrition in patients with SHF increased 2.7 times (OR =4.002, 95% CI: 1.362–10.166).

Table 1 Comparison of the general and clinical data of two groups of patients

Characteristics	Total	Non-malnutrition group, n=137	Malnutrition group, n=105	$Z/t/\chi^2$	P
Gender, n (%)				0.242	0.623
Male	179 (73.97)	103 (75.18)	76 (72.38)		
Female	63 (26.03)	34 (24.82)	29 (27.62)		
Age, years, n (%)				6.618	0.010
<70	108 (44.63)	71 (51.82)	37 (35.24)		
≥70	134 (55.37)	66 (48.18)	68 (64.76)		
BMI, kg/m^2,n (%)				3.638	0.303
<18	3 (1.24)	0 (0.00)	3 (2.86)		
18–24	142 (58.68)	82 (59.85)	60 (57.14)		
24–27.5	66 (27.27)	38 (27.74)	28 (26.67)		
>27.5	31 (12.81)	17 (12.41)	14 (13.33)		
MAMC, n (%)				1.096	0.295
Abnormal	92 (38.02)	56 (40.88)	36 (34.29)		
Normal	150 (61.98)	81 (59.12)	69 (65.71)		
Smoking history, n (%)				3.057	0.080
No	133 (54.96)	82 (59.85)	51 (48.57)		
Yes	109 (45.04)	55 (40.15)	54 (51.43)		
History of diabetes, n (%)				1.066	0.302
No	194 (80.17)	113 (82.48)	81 (77.14)		
Yes	48 (19.83)	24 (17.52)	24 (22.86)		
History of hypertension, n (%)				0.000	0.986
No	173 (71.49)	98 (71.53)	75 (71.43)		
Yes	69 (28.51)	39 (28.47)	30 (28.57)		
Alcohol history, n (%)				1.088	0.297
No	143 (59.09)	77 (56.20)	66 (62.86)		
Yes	99 (40.91)	60 (43.80)	39 (37.14)		
Pulmonary function grading, n (%)				1.723	0.632
1	96 (39.67)	55 (40.15)	41 (39.05)		
2	104 (42.98)	60 (43.80)	44 (41.90)		
3	38 (15.70)	21 (15.33)	17 (16.19)		
4	4 (1.65)	1 (0.73)	3 (2.86)		
Cardiac function grading, n (%)				6.931	0.031
Normal	144 (59.50)	91 (66.42)	53 (50.48)		
Diastolic HF	73 (30.17)	36 (26.28)	37 (35.24)		
Systolic HF	25 (10.33)	10 (7.30)	15 (14.28)		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total	Non-malnutrition group, n=137	Malnutrition group, n=105	Z/t/χ^2	P
Pain grading on admission, n (%)				7.029	0.071
0	149 (61.57)	92 (67.15)	57 (54.29)		
1	52 (21.49)	28 (20.44)	24 (22.86)		
2	27 (11.16)	13 (9.49)	14 (13.33)		
3	14 (5.79)	4 (2.92)	10 (9.52)		
Grading of self-care ability on admission, n (%)				1.084	0.781
0	92 (38.02)	52 (37.96)	42 (40.00)		
1	103 (42.56)	59 (43.07)	44 (41.90)		
2	32 (13.22)	17 (12.41)	15 (14.29)		
3	13 (5.37)	9 (6.57)	4 (3.81)		
Neoadjuvant, n (%)				0.063	0.969
No	168 (69.42)	96 (70.07)	72 (68.57)		
Yes	74 (30.58)	41 (29.93)	33 (31.43)		
Surgical method, n (%)					
LAG	180 (74.38)	104 (78.10)	76 (72.38)	1.055	0.304
TLG	62 (25.62)	30 (21.90)	29 (27.62)		
Surgical scope, n (%)				2.064	0.356
LTG	146 (60.33)	78 (56.90)	68 (64.76)		
LPG	37 (15.29)	21 (15.33)	16 (15.24)		
LDG	59 (24.38)	38 (27.77)	21 (20.00)		
TNM stage, n (%)				19.578	<0.001
I	68 (28.10)	50 (36.49)	18 (17.15)		
II	106 (43.80)	62(45.26)	44 (41.90)		
III	68 (28.10)	25 (18.25)	43 (40.95)		
Degree of differentiation, n (%)				2.777	0.249
Good differentiation	98 (40.50)	50 (36.50)	48 (45.71)		
Moderate differentiation	111 (45.87)	65 (47.45)	46 (43.81)		
Poor differentiation	33 (13.64)	22 (16.06)	11 (10.48)		
C-reactive protein, M [P25, P75]	5.75 [3.30, 11.97]	5.50 [3.30, 10.30]	5.90 [3.50, 17.60]	0.056	0.056
Glycosylated hemoglobin, M [P25, P75]	5.50 [4.90, 6.10]	5.60 [4.90, 6.10]	5.50 [4.90, 5.80]	–0.853	0.394
Carcinoembryonic antigen, M [P25, P75]	3.29 [1.61, 6.72]	2.91 [1.53, 5.66]	3.77 [1.89, 13.26]	–2.775	0.006
Alb, M [P25, P75]	37.15 [33.00, 39.90]	38.30 [34.70, 40.70]	35.40 [31.10, 38.10]	–4.579	<0.001
PAB, M [P25, P75]	220.00 [176.50, 263.00]	245.00 [205.00, 279.00]	186.00 [157.00, 214.00]	–7.657	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total	Non-malnutrition group, n=137	Malnutrition group, n=105	Z/t/χ^2	P
Triglycerides, M [P25, P75]	1.26 [0.94, 1.63]	1.31 [0.99, 1.72]	1.18 [0.88, 1.54]	−2.172	0.033
ALT, M [P25, P75]	18.00 [12.00, 28.00]	19.00 [13.00, 28.00]	17.00 [11.00, 27.00]	−1.268	0.205
AST, M [P25, P75]	21.00 [17.00, 31.00]	20.00 [16.00, 30.00]	24.00 [18.00, 32.00]	−1.934	0.053
Creatinine, M [P25, P75]	65.00 [53.00, 78.00]	64.00 [55.00, 76.00]	65.00 [51.00, 81.00]	−0.200	0.841
Urea nitrogen, M [P25, P75]	5.54 [4.52, 6.91]	5.57 [4.70, 6.82]	5.42 [4.12, 7.45]	−0.809	0.419
Serum sodium, M [P25, P75]	140.90 [139.40, 143.07]	141.30 [139.70, 143.00]	140.50 [138.90, 143.20]	−1.825	0.068
Serum potassium, M [P25, P75]	4.02 [3.72, 4.32]	4.01 [3.73, 4.30]	4.05 [3.70, 4.34]	−0.525	0.599
Hemoglobin, M [P25, P75]	108.00 [82.25, 130.00]	113.00 [87.00, 132.00]	103.00 [73.00, 127.00]	−2.400	0.016
NLR, M [P25, P75]	2.54 [1.77, 4.21]	2.48 [1.58, 3.58]	2.92 [1.92, 5.39]	−2.680	0.007
Adjuvant chemotherapy, n (%)				1.990	0.738
No	23 (9.50)	15 (10.95)	8 (7.62)		
Incomplete	53 (21.90)	33 (24.09)	20 (19.05)		
Complete	166 (68.88)	89 (64.96)	77 (74.04)		
Postoperative complications, n (%)				1.220	0.269
No	210 (86.78)	116 (84.67)	94 (89.52)		
Yes	32 (13.22)	21 (15.33)	11 (10.48)		
EN within Post-op 48 h, n (%)				3.721	0.054
Yes	169 (69.83)	103 (75.18)	66 (62.86)		
No	73 (30.17)	34 (24.82)	39 (37.14)		

BMI, body mass index; MAMC, mid-arm muscle circumference; HF, heart failure; LAG, laparoscopic assisted radical gastrectomy; TLG, total laparoscopic radical gastrectomy; LTG, laparoscopic total gastrectomy; LPG, laparoscopic proximal gastrectomy; LDG, laparoscopic distal gastrectomy; TNM, Tumor node metastasis; Alb, albumin; PAB, prealbumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NLR, neutrophil-to-lymphocyte ratio; EN, enteral nutrition; Post-op, postoperative.

NLR was an independent risk factor for malnutrition (OR =1.120, 95% CI: 1.006–1.247), while PAB and EN within 48 h post-op were independent protective factors (OR =0.979, 95% CI: 0.975–0.985; OR =0.472, 95% CI: 0.232–0.958). There was no statistical collinearity between the variables (TOL <1, 1< VIF <10). The Youden index of the predictive model was 0.536, and the C-index was 0.82 (95% CI: 0.79–0.89; *Table 2* and *Figure 2*).

The multivariate logistic regression equation was as follows:

$$\begin{aligned} Y=&3.527+0.55\times \text{TNM II}+1.27\times \text{TNM III} \\ &+0.49\times \text{DHF}+1.48\times \text{SHF}-0.02\times \text{PAB} \\ &+0.12\times \text{NLR}-0.81\times \text{EN within 48 h Post-op}. \end{aligned} \quad [1]$$

P=Y/1+Y and P>0.536 implied the occurrence of three-month-postoperative malnutrition.

Construction of a nomogram of the prediction model

The five independent variables in the prediction model (TNM stage, CFG, PAB, NLR, and EN within 48 h post-op) were employed to construct a nomogram, as illustrated in *Figure 2*.

To interpret the nomogram, a vertical line was drawn on the horizontal axis where each independent variable index of a patient was located, and the value on the horizontal axis of the corresponding "Point" was a specific score. Scores corresponding to the five independent variables were added to obtain the total score, and a vertical line then drawn downward. The predicted value on the horizontal axis

Table 2 Multivariate logistic regression analysis of malnutrition after gastric cancer surgery

Variables	β	SD	P	OR	95% CI		TOL	VIF
					Lower	Upper		
TNM I (DV)			0.020				0.928	1.077
TNM II	0.554	0.403	0.170	1.740	0.789	3.837		
TNM III	1.266	0.455	0.005	3.547	1.454	8.651		
CFG normal (DV)			0.013				0.990	1.010
CFG DHF	0.487	0.370	0.189	1.627	0.788	3.360		
CFG SHF	1.475	0.510	0.004	4.369	1.607	11.876		
PAB	–0.022	0.003	<0.001	0.979	0.972	0.985	0.933	1.072
NLR	0.122	0.055	0.027	1.130	1.014	1.259	0.969	1.032
EN within 48 h post-op	–0.808	0.361	0.025	0.446	0.220	0.904	0.918	1.089

SD, standard deviation; OR, odds ratio; CI, confidence interval; TOL, tolerance; VIF, variance inflation factor; TNM, tumor node metastasis; DV, dummy variable; CFG, cardiac function grading; DHF, diastolic heart failure; SHF, systolic heart failure; PAB, prealbumin; NLR, neutrophil-to-lymphocyte ratio; EN, enteral nutrition; post-op, postoperative.

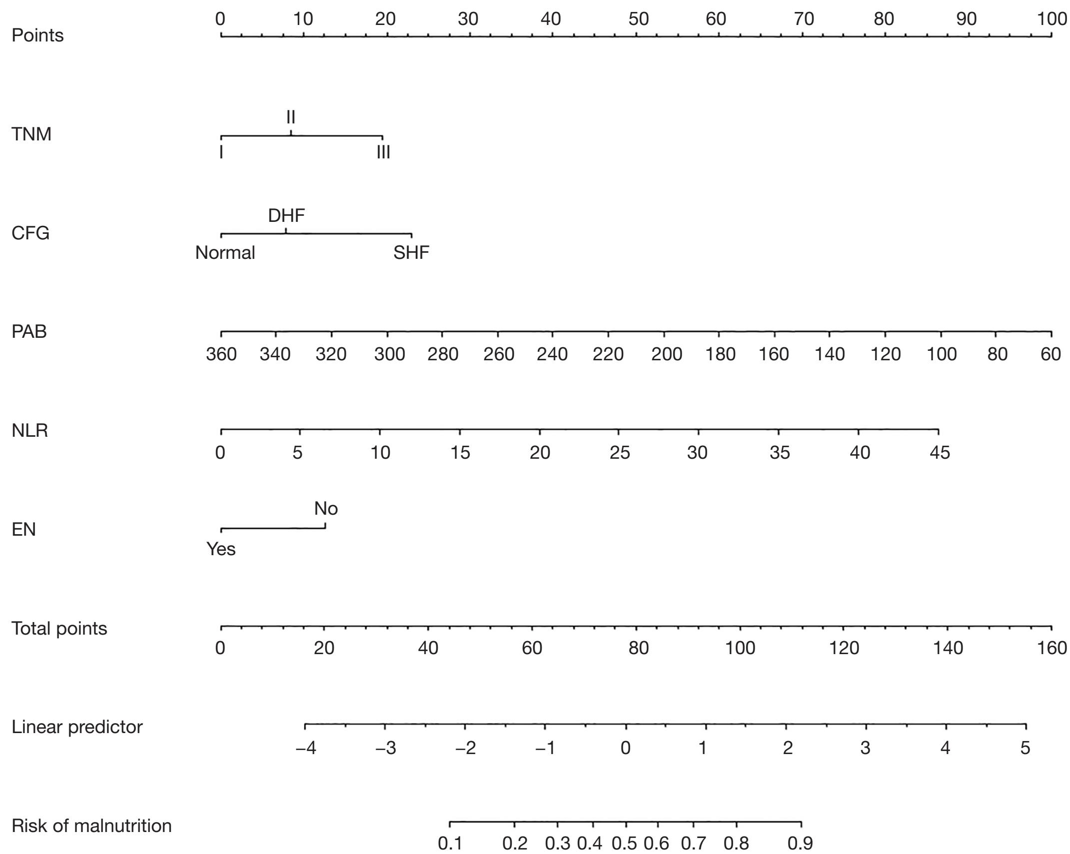

Figure 2 Nomogram for the prediction model of malnutrition after gastric cancer surgery. TNM, tumor node metastasis; CFG, cardiac function grading; PAB, prealbumin; NLR, neutrophil-to-lymphocyte ratio; EN, enteral nutrition.

corresponding to "Risk" was the predicted value of the risk of the patient.

Balanced comparison between the training and validation sets

The difference test revealed no statistical difference in the general and perioperative data between the training and validation sets (P>0.05), confirming the two data sets were comparable (*Table 3*).

Evaluation of the predictive performance (discrimination) of the model

The AUCs of the model in the training and validation sets were 0.840 (95% CI: 0.787–0.884) and 0.854 (95% CI: 0.770–0.916), respectively, and both values were better than those of the NRS2002 (AUC: 0.757, 95% CI: 0.698–0.809) in the training set. The AUC of the training set prediction model was significantly higher than that of the NRS2002 scale (Z value=2.184, P=0.029). These results indicated the model had good differentiation in predicting the risk of malnutrition three months after gastric cancer surgery (*Figure 3*).

Evaluation of the calibration degree of the model

Through visual observation, the predicted probability in the calibration curve of training and test sets was determined to be highly consistent with the actual probability (*Figure 4*). The Brier scores of the training and validation sets were 0.159 and 0.195, respectively, and the Hosmer-Lemeshow tests revealed no statistically significant deviation between the predicted and actual values of risk for the training (χ^2=14.070, P=0.08) and validation sets (χ^2=1.989, P=0.98). The above parameters verified the model had high prediction accuracy.

Evaluation of the clinical applicability of the model

The clinical applicability of the model was evaluated by drawing a clinical decision curve analysis (DCA). The results suggested that when the threshold probability of three-month-postoperative malnutrition in gastric cancer patients predicted by the model nomogram was 10–85%, the clinical net benefit of the model was good (good clinical applicability), which is superior to the "full intervention" or "no intervention" scheme. The threshold probability was 10–75%, and the clinical net benefit of this model was better than that of NRS2002 scale (*Figure 5*).

Discussion

Malnutrition indicates chronic nutritional deficiencies in the body caused by insufficient food intake, impaired digestion and absorption, and excessive wastage during the process of ingesting nutrients. The risk of malnutrition elucidates the impact of undernutrition on adverse clinical events or outcomes in patients. Huang *et al.* retrospectively analyzed 597 older adult patients (>60 years old) who underwent radical gastrectomy for gastric cancer, and approximately 34.5% presented postoperative malnutrition (18). Skeie *et al.* retrospectively analyzed 6,110 patients in Norway's National Gastric Cancer Surgery Registry using Global Leadership Initiative on Malnutrition (GLIM) criteria, and discovered 35.4% of the patients had postoperative malnutrition, of whom 15.6% were severely malnourished (19). Thus, it can be seen that postoperative patients with gastric cancer are prone to malnutrition. The reasons for ths stem from two main factors. The first is the influence of gastric cancer itself on the nutritional status of the body, and the second relates to the impact of surgery on nutritional status. Additionally, patients with malnutrition after gastric cancer surgery generally develop adverse body states such as low tissue protein levels, impaired immune function, and internal environment disturbances, which make them prone to severe complications such as postoperative infection and poor anastomotic healing (20). Malnourished patients also have a decreased willingness and ability to exercise postoperatively, resulting in muscle atrophy and decreased intestinal motility (21). All the above issues tend to aggravate the malnutrition state of the patient, forming a vicious circle. Xiao *et al.* reported that nutritional deficiencies following gastric cancer surgery directly impact the treatment effect of patients and can easily lead to adverse clinical outcomes (22).

In this study, the timepoint of three months after surgery was selected as the period for assessment of malnutrition and as the basis for grouping. The reasons for choosing this timepoint are threefold. (I) The first is the high incidence of malnutrition and the stability of results in this period. Hirahara *et al.* revealed the peak period of malnutrition occurred three months after gastric cancer surgery, as the dietary structure and nutritional status of most patients are basically fixed at this time, and the evaluation results are relatively reliable (13). In addition, the survival analysis of

Table 3 Comparison of general and clinical data between the training set and validation set

Characteristics	Training set, n=242	Validation set, n=102	Z/t/χ^2	P
Gender, n (%)			1.425	0.233
Male	179 (73.97)	69 (67.65)		
Female	63 (26.03)	33 (32.35)		
Age, years, n (%)			0.171	0.679
<70	108 (44.63)	48 (47.06)		
≥70	134 (55.37)	54 (52.94)		
BMI, kg/m^2, n (%)			4.179	0.243
<18	3 (1.24)	3 (2.94)		
18–24	142 (58.68)	50 (49.02)		
24–27.5	66 (27.27)	30 (29.41)		
>27.5	31 (12.81)	19 (18.63)		
MAMC, n (%)			3.584	0.058
Abnormal	92 (38.02)	50 (49.02)		
Normal	150 (61.98)	52 (50.98)		
Smoking history, n (%)			0.709	0.400
No	133 (54.96)	51 (50.00)		
Yes	109 (45.04)	51 (50.00)		
History of diabetes, n (%)			1.853	0.173
No	194 (80.17)	75 (73.53)		
Yes	48 (19.83)	27 (26.47)		
History of hypertension, n (%)			1.778	0.182
No	173 (71.49)	80 (78.43)		
Yes	69 (28.51)	22 (21.57)		
Alcohol history, n (%)			0.949	0.330
No	143 (59.09)	66 (64.71)		
Yes	99 (40.91)	36 (35.29)		
Pulmonary function grading, n (%)			6.683	0.083
1	96 (39.67)	45 (44.12)		
2	104 (42.98)	41 (40.20)		
3	38 (15.70)	10 (9.80)		
4	4 (1.65)	6 (5.88)		
Cardiac function grading, n (%)			0.239	0.887
Normal	144 (59.50)	63 (61.76)		
Diastolic HF	73 (30.17)	30 (29.41)		
Systolic HF	25 (10.33)	9 (8.83)		

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Training set, n=242	Validation set, n=102	Z/t/χ^2	P
TNM stage, n (%)			0.249	0.883
I	68 (28.10)	30 (29.41)		
II	106 (43.80)	46 (45.10)		
III	68 (28.10)	26 (25.49)		
Pain grading on admission, n (%)			1.198	0.754
0	149 (61.57)	61 (59.8)		
1	52 (21.49)	19 (18.63)		
2	27 (11.16)	15 (14.71)		
3	14 (5.79)	7 (6.86)		
Grading of NRS2002 on admission, n (%)			2.037	0.153
<3	184 (76.03)	70 (68.63)		
≥3	58 (23.97)	32 (31.37)		
Grading of self-care ability on admission, n (%)			2.750	0.432
0	92 (38.02)	45 (44.12)		
1	103 (42.56)	42 (41.18)		
2	32 (13.22)	8 (7.84)		
3	13 (5.37)	7 (6.86)		
Alb, M [P25, P75]	37.15 [33.00, 39.90]	37.20 [34.65, 39.50]	0.490	0.624
Prealbumin, M [P25, P75]	220.00 [176.50, 263.00]	225.50 [183.00, 266.00]	0.747	0.455
Neutrophils/lymphoc, M [P25, P75]	2.55 [1.76, 4.23]	2.63 [1.67, 4.35]	0.177	0.860
Neoadjuvant, n (%)			0.046	0.830
No	168 (69.42)	72 (70.59)		
Yes	74 (30.58)	30 (29.41)		
Surgical method, n (%)			0.047	0.829
LAG	160 (66.12)	70 (68.63)		
TLG	82 (33.88)	32 (31.37)		
Surgical scope, n (%)			0.055	0.973
LTG	135 (55.79)	61 (59.80)		
LPG	37 (15.29)	15 (14.71)		
LDG	70 (28.93)	26 (25.49)		
Adjuvant chemotherapy, n (%)			0.241	0.883
Good differentiation	98 (40.50)	43 (40.50)		
Moderate differentiation	111 (45.87)	47 (44.76)		
Poor differentiation	33 (13.64)	12 (11.76)		

Table 3 (*continued*)

Table 3 *(continued)*

Characteristics	Training set, n=242	Validation set, n=102	Z/t/χ^2	P
Postoperative complications, n (%)			3.776	0.052
No	210 (86.78)	80 (78.43)		
Yes	32 (13.22)	22 (21.57)		
EN within 48 h post-op, n (%)			0.002	0.967
Yes	169 (69.83)	71 (69.61)		
No	73 (30.17)	31 (30.39)		

BMI, body mass index; MAMC, mid-arm muscle circumference; HF, heart failure; TNM, tumor node metastasis; NRS2002, nutritional risk screening 2002; Alb, albumin; LAG, laparoscopic assisted radical gastrectomy; TLG, total laparoscopic radical gastrectomy; LTG, laparoscopic total gastrectomy; LPG, laparoscopic proximal gastrectomy; LDG, laparoscopic distal gastrectomy; EN, enteral nutrition; Post-op, postoperative.

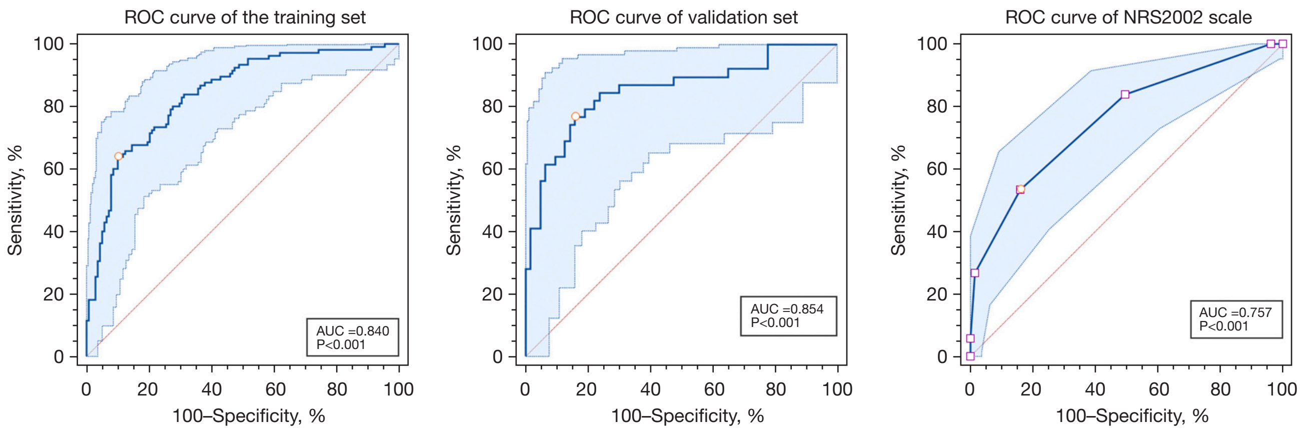

Figure 3 ROC curve between the prediction model of postoperative malnutrition in gastric cancer and NRS2002. ROC, receiver operating characteristic; AUC, area under curve; NRS2002, nutritional risk screening 2002.

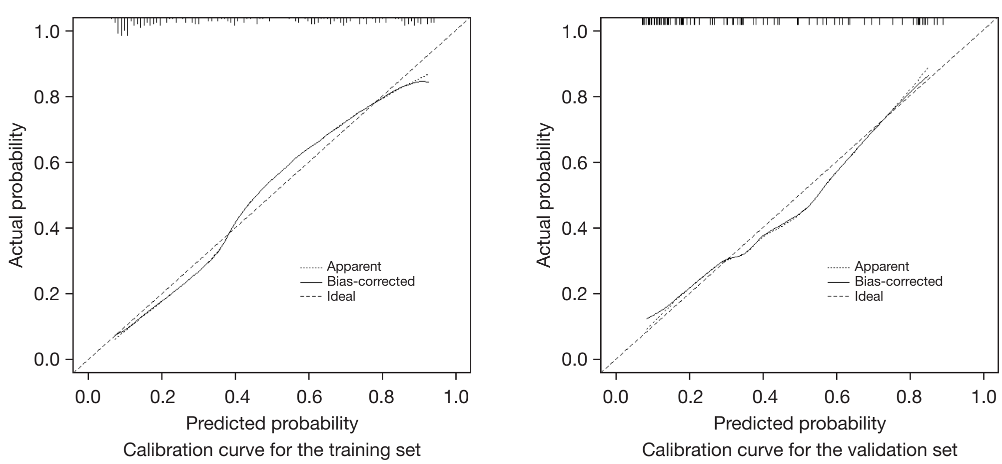

Figure 4 Calibration curve of a predictive model for post-surgical malnutrition in gastric cancer.

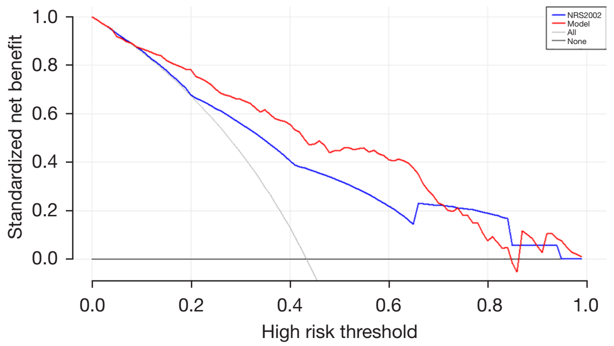

Figure 5 Decision curve analysis of a predictive model for post-surgical malnutrition in gastric cancer. NRS2002, nutritional risk screening 2002.

Fujiya *et al.* examining postoperative malnutrition in gastric cancer showed the risk of malnutrition three months after surgery (HR: 2.18) was higher than at one month (HR: 1.77) and six months (HR: 1.81) (14). (II) The time effect makes it difficult for patient status indicators at admission or during perioperative period to have an impact six months after surgery (7). (III) Some patients with gastric cancer still have not completely restored their normal diet one month after surgery, and it is easy to obtain false positive results by utilizing nutritional status at this time as a reference (23). Subsequently, this study included the significant variables in the difference test and those that may have an impact on the outcome in the clinical opinion in the logistic regression. The findings showed only TNM stage, CFG, PAB, NLR, and EN within 48 h post-op had statistical significance in the multivariate analysis screen, which is due to the following: (I) The sample size was limited. Although there are several factors (such as chemotherapy status, including neoadjuvant chemotherapy and postoperative chemotherapy) that are believed to have an influence in clinical outcomes, they have theoretical connections with malnutrition outcomes and show a certain trend of difference in descriptive statistics. However, there was no statistical significance in univariate and multivariate analysis, which may be related to the limited sample size of this study (24). (II) There may be a confounding effect. Although some variables showed differences in the univariate analysis, there is a possibility of an intermediary effect (such as albumin and PAB) with the outcome from the mechanism perspective. In the multivariate analysis, after removing the confounding factors, it failed to show an independent impact on the outcome (25). (III) In contrast, the variable EN within 48 h post-op has a theoretical mechanism that affects postoperative nutrition status. In the univariate analysis, the correlation between this variable and outcome was affected by other variables, presenting a comprehensive result. After eliminating the influence of other variables (such as underestimating the negative confounding of this variable and outcome) through multivariate analysis, it was found that EN within 48 h post-op had an independent effect (25). Finally, this study selected the above five variables to establish the model. From the clinical point of view, the variables in the model meet the multi-dimensional requirements and can reflect the pathophysiological state of the body through the tumor itself (TNM stage) as well as the cardiac function (CFG), nutritional reserve (PAB), body inflammation or stress degree (NLR), and intestinal function (EN within 48 h post-op) of gastric cancer patients during the perioperative period. Moreover, they can jointly predict the outcome from multiple angles. In addition, the five variables in the model were theoretically related to the clinical outcome of malnutrition, taking into consideration both statistical results and disease pathogenesis.

The TNM stage of gastric cancer was adopted as a standard to evaluate the degree of infiltration and metastasis of the tumor itself, with a higher stage indicating a higher degree of malignancy. This study shows the risk of postoperative malnutrition in patients with TNM III is significantly increased. Gastric cancer associated with TNM III may penetrate the serous layer and invade the surrounding lymph nodes and tissues over a large area, leading to digestive and absorption dysfunction in patients. Cancer cells compete with normal cells in the body for nutrients and consume significant amounts of energy and protein. Moreover, patients with a high TNM stage usually develop accompanying symptoms such as anorexia, pain, nausea, and vomiting, resulting in insufficient intake. Such patients require wider surgical resection and longer courses of adjuvant chemotherapy, increasing the risk of postoperative malnutrition. Ravasco *et al.* suggested the malignant degree of gastric cancer was a critical factor affecting the nutritional status of patients, and TNM staging was an effective clinical indicator to evaluate the degree of malignancy (26). Lee *et al.* demonstrated the malignant degree of gastric cancer was closely correlated with the occurrence of postoperative malnutrition and was an independent risk factor (27). In this study, considering TNM IV patients, the influence of tumor-related factors on postoperative malnutrition may be far greater than other factors related to patients themselves. Tumors with distant metastasis have a great impact on body function, material metabolism and organ function, and secondary complications and serious abnormalities of related indicators, and most of these patients have lost the opportunity for surgery. Furthermore, there is a bias in selection. To avoid statistical selection bias, we excluded it at the research design stage.

In this study, the cardiac function classification (CFG) was based on the parameters of cardiac color ultrasound. According to LVEF and whether diastolic dysfunction is present, cardiac function is divided into three grades. Multivariate analysis showed that the risk of postoperative malnutrition in patients with heart failure with LVEF ≤40% was significantly higher than in patients with gastric cancer and normal cardiac function. Kinugawa and Lin *et al.* suggested patients with chronic heart failure frequently suffer from malnutrition ascribed to changes in systemic metabolism and increased body consumption, with an incidence rate of 16–62% (28,29). Patients undergoing gastric cancer surgery are more likely to suffer from insufficient body intake, loss of appetite, and increased risk of postoperative malnutrition because of reduced intake and exercise tolerance, especially if complicated by cardiac insufficiency. Sze *et al.* showed chronic heart failure aggravates the symptoms of gastrointestinal congestion and intestinal edema in patients with gastric cancer, impacts the absorption of nutrients, and increases the occurrence of malnutrition (30).

PAB is synthesized by hepatocytes and is so named because it is generally displayed in front of albumin by electrophoresis. Owing to its short half-life of only12 hours, it is more sensitive than albumin and transferrin in response to malnutrition. Moreover, in this study, after logistic regression corrected for confounding factors, PAB was still an independent protective factor for postoperative malnutrition, and its specificity was stronger than that of albumin and hemoglobin. Aoyama *et al.* reported that prealbumin can be used as a representative indicator of postoperative nutritional status in patients with gastric cancer and is correlated with recurrence and survival rates (31), and Zu *et al.* confirmed that the level of prealbumin at admission is an independent risk factor for the long-term prognosis of gastric cancer patients (32).

NLR is an indicator of the degree of inflammation in the body, and this study observed it as an independent risk factor for malnutrition after gastric cancer surgery. One reason for this may be because the more intense the inflammatory response of gastric cancer patients, the greater the consumption of nutrients, and the more likely this is to aggravate stress trauma, such as that associated with surgery, increase the chance of postoperative infection, and promote the occurrence of postoperative malnutrition status (33). Another reason concerns neutrophils, which can drive tumor growth and metastasis by producing soluble cytokines, various proteases, and inhibiting functions of effector T cells and NK cells (34). A decrease in the number of lymphocytes implies a decrease in immune function and surveillance, making it easier for tumors to metastasize (35). The accelerated growth or metastasis of gastric cancer directly aggravates the consumption of nutrients and obstructs digestion and absorption functions.

Early postoperative EN is an important part of accelerated rehabilitation in patients with gastric cancer. This study shows that EN within 48 hours after gastrectomy can significantly reduce the risk of malnutrition three months after surgery. Laparoscopic radical gastrectomy may cause stress irritation to intestinal mucosa and lead to mucosal ischemic injury and even necrosis, causing intestinal dysfunction, affecting material absorption and metabolism, and promoting bacterial migration (36). Early EN can stimulate the secretion of gastrointestinal hormones by mucosa, promote the recovery of intestinal peristalsis and digestive function after operation, and shorten the exhaust time (37). In addition, EN includes arginine, glutamine ω-3PUFA, and antioxidant micronutrients that can repair and maintain the intestinal mucosal barrier and ensure structural and functional integrity (38). EN also provides heat and nitrogen sources, promotes the synthesis of total proteins and stress proteins, corrects the negative nitrogen balance, improves immune capacity, and reduces postoperative inflammatory reactions. Carmichael *et al.* showed that EN within 48 hours after gastrectomy can effectively improve the nutritional status of patients (39).

In terms of model display, this study intuitively expressed the meaning of the model in the form of a nomogram and quantified risks concisely and effectively, which is convenient for clinical use. In the design method, the included patients were divided into a training set and a validation set under the condition that the baseline conditions of the two data sets were comparable. The model discrimination was evaluated using the ROC curve, and the obtained AUC values of the two sets were 0.840 and 0.854, respectively. According to the standard of AUC prediction validity, the overall discrimination of the prediction model was good. Compared with the commonly used NRS2002 scale, the model had higher validity in predicting malnutrition after gastric cancer surgery, and its prediction accuracy was confirmed by the calibration curve (visual observation, Brier value: 0.161, 0.195) and the Hosmer-Lemeshow goodness-of-fit test (P>0.05). The DCA curve demonstrated the predicted probability of this model was in the range of 10–85%, that the level of clinical net benefit was the highest, and that the model possessed acceptable clinical applicability, better than the NRS2002 scale. In addition, the variables in the prediction model were commonly used clinical classification or laboratory indicators which can be quickly applied in clinical practice. Based on the predictive effect of the risk model and the clinical significance of the variables in the model, this model has the following clinical guiding significance for improving the postoperative malnutrition status of gastric cancer and reducing its incidence or impact: (I) Early warning and early intervention. Especially for patients with late TNM stage, scientific nutrition support plan can be formulated in collaboration with the nutrition department during the perioperative period; (II) Ameliorate the patient's cardiac function, reduce the cardiac load before operation and improve activity tolerance; (III) Improve the preoperative nutritional status of patients and increase nutrition and energy reserves; (IV) Reduce the inflammatory reaction of patients before operation and actively treat infection complications; (V) Open enteral nutrition within 48 hours after operation to increase intestinal peristalsis and protect intestinal mucosal barrier. Therefore, the prediction model can provide not only early warning for high-risk patients with malnutrition after gastric cancer surgery but also theoretical support and practical guidance for early intervention in high-risk patients.

However, this study, as a retrospective analysis of a single center, has limitations. First, the number of cases is small, and the source is limited. Second, the established model needs to be verified through an in-depth prospective cohort study. Third, the selected indicators did not include an evaluation of the patients' families, including socioeconomic status, types of meals, and eating habits. Therefore, we expect to conduct a multi-center prospective study incorporating more innovative indicators to further improve the predictive performance of the model.

Conclusions

In this study, the statistical method of multivariate regression was used to identify the risk factors and establish the prediction model for malnutrition three months after gastrectomy in patients with gastric cancer. Moreover, a variety of statistical strategies were used to verify the model externally. The results proved the model has good prediction efficiency and clinical scalability and can effectively predict the occurrence of malnutrition three months after gastric cancer surgery while guiding early intervention plans.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1307/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1307/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1307/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of the Second Hospital of Anhui Medical University (No. YX-2022-158) and informed consent was taken from all the patients.

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