Original Article
Prognostic nutritional index combined with carcinoembryonic antigen and carbohydrate antigen 242 for early prediction of anastomotic leakage after radical gastrectomy for gastric cancer

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Abstract: Objective: To observe the clinical value of prognostic nutritional index (PNI) combined with carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 242 in early prediction of anastomotic leakage after radical gastrectomy for gastric cancer. Methods: We retrospectively collected clinical data of 350 gastric cancer patients who underwent radical gastrectomy in Gansu Provincial Hospital of Traditional Chinese Medicine between January 2018 and May 2022. According to the occurrence of anastomotic leakage, patients were divided into an occurrence group (n=34) and a non-occurrence group (n=316). The clinical value of PNI combined with CEA and CA242 on the 3rd day after surgery in predicting anastomotic leakage was explored. Lasso regression analysis was used to screen predictive indicators of anastomotic leakage and establish a risk model. Results: In the 350 patients who underwent radical gastrectomy for gastric cancer, anastomotic leakage was observed in 34 cases, with an incidence rate of 9.7%. A higher proportion of patients in the occurrence group exhibited diabetes, hand-sewn anastomosis, advanced tumor node metastasis (TNM) staging, and intraoperative bleeding, when compared to those in the non-occurrence group (P<0.05). Moreover, on the 3rd postoperative day, patients in the occurrence group demonstrated a significantly lower PNI than those in the non-occurrence group, along with elevated levels of CEA and CA242 (P<0.05). The area under the curve (AUC) for PNI, CEA, and CA242 were 0.827, 0.601, and 0.504, respectively, while the AUC for the combination was 0.829. As per the LASSO regression analysis, history of diabetes and PNI were identified as key factors correlating with anastomotic leakage (P<0.05). Employing the risk score formula, we obtained individual risk scores for each sample. Notably, risk scores in the occurrence group significantly surpassed those in the non-occurrence group (P<0.0001). The AUC for the risk score in predicting patient lung infection was 0.854. The internal verification C-index emerged as 0.863 (0.806-0.920), indicating a good model fit. Furthermore, the DeLong test revealed a significantly greater AUC of the risk model, compared to the combination and PNI (P<0.05). Conclusion: CEA and CA242 are not promising predictive indicators for anastomotic leakage after surgery in patients with gastric cancer, but the prediction model we established can improve the predictive efficiency of anastomotic leakage in these patients.

Keywords: Prognostic nutritional index (PNI), carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 242, anastomotic leakage after radical gastrectomy for gastric cancer

Introduction

Gastric cancer is a highly prevalent malignant tumor worldwide, with its incidence ranking second among all types of malignant tumors and its mortality ranking third in China [1]. Despite significant advancements in modern chemotherapy and radiotherapy, radical gastrectomy remains the primary treatment choice for advanced gastric cancer [2]. Early postoperative complications include bleeding, anastomotic leakage, and intestinal obstruction. Among these, anastomotic leakage is the most severe and requires significant attention, as it can result in a mortality of up to 30% [3].

Although treatment outcomes for anastomotic leakage have improved, the mortality associat-

ed with this complication still persists at around 15% [4]. Early diagnosis and intervention are critical in enhancing patients' postoperative quality of life and reducing the economic burden and hospital stay, as well as in decreasing mortality from postoperative complications [5, 6]. However, surgery provokes a robust inflammatory response, manifesting as fever, leukocytosis, rapid breathing, and fast heartbeat, and other syndromes. This complicates the prediction of anastomotic leakage via clinical symptoms [7, 8] and impedes the implementation of early interventions.

While auxiliary examinations like CT and B-ultrasound, as well as abdominal examinations, can diagnose anastomotic leakage [9], there are often misdiagnosis and false negatives. With the evolution of various anastomotic devices and the prevalent use of high-quality sutures, the reliability of detecting postoperative anastomotic leakage has significantly improved, making immediate postoperative leakage a rarity. Furthermore, due to individual variability, the timing of postoperative anastomotic leakage can be different, typically occurring around the 6th day after surgery but potentially appearing as late as 2 weeks or even 1 month post-surgery [10, 11]. Thus, effective biochemical markers are needed for the early screening and monitoring of anastomotic leakage.

The prognostic nutritional index (PNI) is a measure reflecting a patient's nutritional and immune status. It was first proposed by Buzby et al. in 1980 to assess nutritional status and surgical risk [12, 13]. Although some research suggests a connection between PNI and anastomotic leakage, uncertainties still exist. For instance, a study by A-Lai et al. [14] found that preoperative PNI held no significant prognostic value for short-term prognosis of patients with post-esophagectomy anastomotic leakage. There is limited evidence regarding the predictive value of PNI for anastomotic leakage in patients with gastric cancer.

Consequently, this study aimed to analyze the clinical value of PNI with carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 242 in the early prediction of anastomotic leakage after radical gastrectomy for gastric cancer, thereby providing a reference for clinical practice.

Methods and materials

Ethical statement

This study was approved by the Medical Ethics Committee of Gansu Provincial Hospital of Traditional Chinese Medicine (ethical lot number: 2022 (A) 25).

Sample source

We retrospectively collected the clinical data of 350 patients with gastric cancer who underwent radical gastrectomy in Gansu Provincial Hospital of Traditional Chinese Medicine from January 2018 to May 2022. See **Figure 1** for the study flow chart.

Inclusion and exclusion criteria

Inclusion criteria: patients with complete medical records; patients who were diagnosed with gastric cancer by digestive endoscopic biopsy before operation; patients who underwent radical resection of gastric cancer with D2 lymph node dissection; for patients with anastomotic leakage, and the complication developed between postoperative day 6 and day 30.

Exclusion criteria: patients who required surgery due to emergencies such as gastric perforation or bleeding; patients with distant metastasis or local invasion of adjacent organs, detected by imaging examination or other means; patients who underwent preoperative radiotherapy or chemotherapy; patients with long-term use of immunosuppressants or nonsteroidal anti-inflammatory drugs; patients who underwent combined resection of other organs such as part of the pancreas or spleen; patients who only had palliative surgery; patients who experienced other infectious complications after the operation; patients who underwent intraperitoneal hyperthermic perfusion chemotherapy after the operation.

Diagnostic methods

The diagnostic criteria for anastomotic leakage were as follows. Patients experienced symptoms such as abdominal pain, fever, and signs of abdominal infection. There was evidence of digestive fluid or cloudy fluid discharge from the drainage tube or abdominal wall incision. Patients were asked to use oral melanin to help
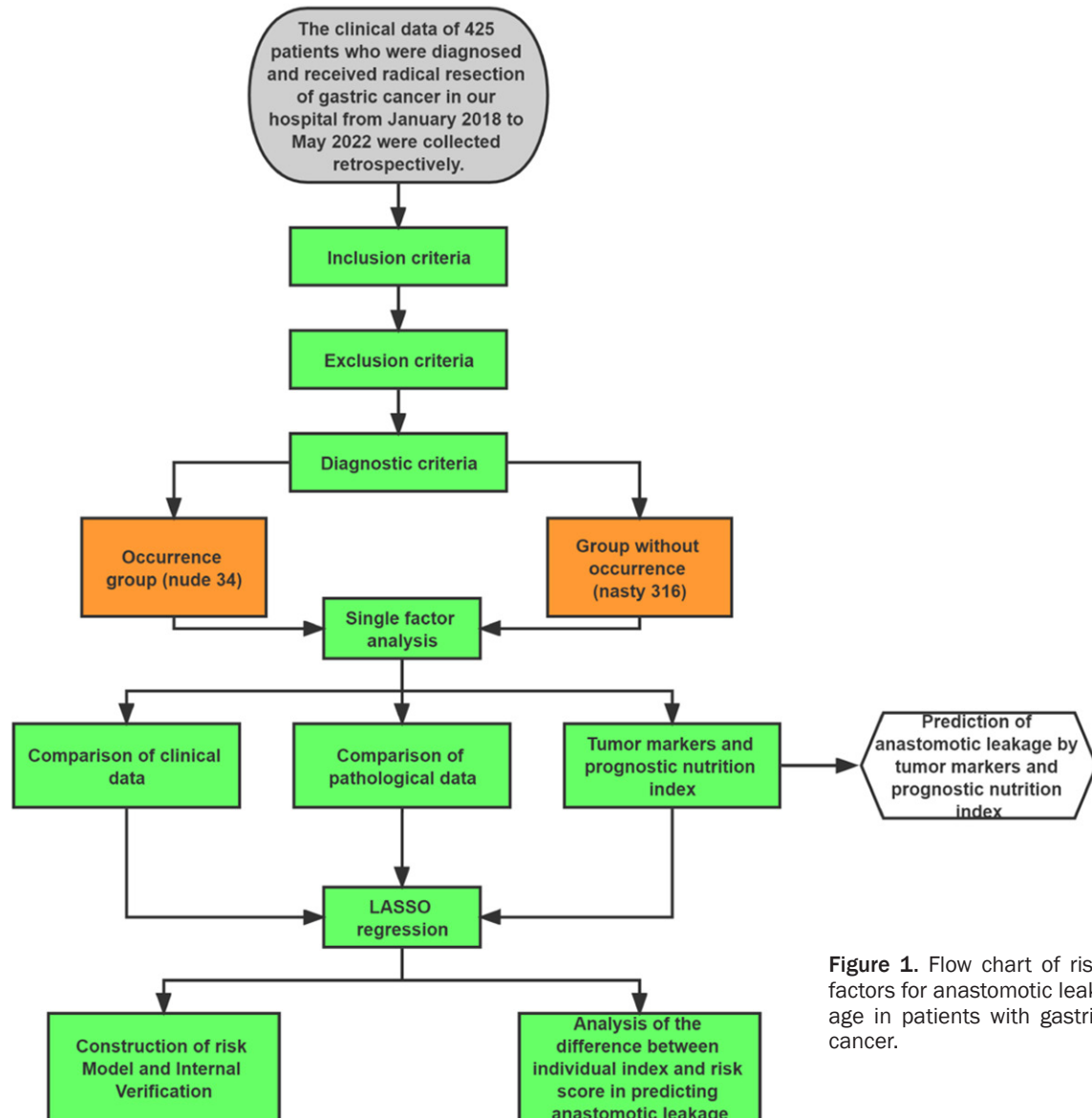
Figure 1. Flow chart of risk factors for anastomotic leakage in patients with gastric cancer.

the observation of leakage from the drainage tube or abdominal wall. X-ray imaging of the upper gastrointestinal tract was performed to confirm the external leak of the digestive tract and to determine the size and occurrence of the anastomotic leak. A CT examination was conducted to assess the conditions around the anastomosis, and to observe whether there was contrast agent leakage together with the gastrointestinal tract imaging. Color ultrasound examination was performed to detect fluid accumulation in the thoracic and abdominal cavity. If there was fluid accumulation, puncture under the guidance of color ultrasound was carried out to extract the digestive fluid or pus.

Sample screening

Based on the inclusion and exclusion criteria, we included 350 among 425 patients. Among the included patients, 34 patients had anastomotic leakage, with an incidence of 9.7%.

Collection of clinical data

The patients' clinical data were collected from the electronic medical records, including age, sex, body mass index (BMI), smoking history, history of hypertension or diabetes, surgical method, surgical resection range, pathological stage, Lauren classification, and pathological

Table 1. Comparison of the clinical data

Variable	Occurrence group (n=34)	Non-occurrence group (n=316)	P value
Age			0.355
≥60 years old	19	205	
<60 years old	15	111	
Sex			0.577
Male	17	174	
Female	17	142	
BMI			0.492
≥25 kg/m^2	9	63	
<25 kg/m^2	26	253	
Smoking History			0.266
Present	15	174	
Absent	19	142	
History of Hypertension			0.434
Present	13	142	
Absent	21	174	
History of Diabetes			<0.0001
Present	16	57	
Absent	18	259	

Note: BMI, Body mass index.

diagnosis. Laboratory indicators included CEA, CA242, and PNI on the third postoperative day. PNI = serum albumin value (g/L) + 5 × lymphocyte total count in peripheral blood (× 10^9/L).

Observation indicators

Primary observation indicators were the expression and predictive value of CEA, CA242, and PNI in patients with anastomotic leakage.

Secondary observation indicators included the clinical data of the two groups, predictors of anastomotic leakage screened by LASSO regression analysis, and a risk model.

Statistical analysis

R language 4.1.1 software (R Foundation for Statistical Computing, Vienna, Austria) was used for data cleaning, data analysis, and model establishment. LASSO regression was used to screen predictive factors with non-zero coefficients, and the clinical value was verified by receiver operating characteristic (ROC) curve. The difference in the areas under the ROC curve was analyzed by Delong test. Graph Pad Prism 8.0 was used for data visualization. Measurement data were represented as (X±S)

and analyzed by the t-test. Count data were expressed in percentage (%) and processed by chi-square test, representing by χ^2. When P<0.05, the differences were considered statistically significant.

Results

Analysis of clinical data

Among the 350 included cases, 34 developed anastomotic leakage, with an incidence of 9.7%. Patients were subsequently divided into two groups: those with anastomotic leakage (occurrence group, n=34) and those without (non-occurrence group, n=316). Further analyses of the clinical data between the two groups revealed a significant higher proportion of patients with diabetes in the occurrence group compared to the non-occurrence group (P<0.05, see **Table 1**). However, no significant differences were found between the two groups in terms of age, sex, BMI, smoking history, and history of hypertension (P>0.05, see **Table 1**).

Analysis of surgical and pathological data

The occurrence group exhibited a higher number of patients with manual anastomosis, higher TNM staging, and intraoperative blood loss compared to the non-occurrence group (P< 0.05, **Table 2A**). No statistical difference was found in the other variables, such as surgical method, resection range, tumor diameter, Lauren classification, and degree of differentiation (P>0.05, **Table 2A**).

Expression of laboratory indicators and prediction of anastomotic leakage

We scrutinized the levels of PNI, CEA, and CA242 on the 3rd day post-surgery in both the occurrence and non-occurrence groups. The results divulged that the PNI in the occurrence group was markedly lower than that in the non-occurrence group (P<0.0001, **Figure 2**). Concurrently, the levels of CEA and CA242 in the occurrence group were higher than those in the non-occurrence group (P<0.05, **Figure 2**). Further investigation using the ROC curve

Table 2A. Analysis of surgical and pathological data

Variable	Occurrence group (n=34)	Non-occurrence group (n=316)	P value
Surgical Method			0.575
Open Surgery	16	133	
Laparoscopic Surgery	18	183	
Extent of Resection			0.611
Proximal Gastrectomy	1	16	
Distal Gastrectomy	26	253	
Total Gastrectomy	7	47	
Anastomosis Method			0.030
Hand-sewn Anastomosis	15	199	
Stapler Anastomosis	19	117	
Tumor Diameter (mm)			0.157
≥30	24	259	
<30	10	57	
TNM Staging			0.014
I	4	92	
II	6	82	
III	24	142	
Lauren Classification			0.842
Intestinal Type	10	82	
Diffuse Type	4	47	
Mixed Type	20	186	
Degree of Differentiation			0.418
Low-grade	14	111	
Medium, High-grade	20	205	
Intraoperative Blood Loss (mL)			0.002
≥400	26	152	
<400	9	164	

Note: TNM, tumor node metastasis.

unveiled that the area under the curve (AUC) for PNI, CEA, and CA242 was 0.827, 0.601, and 0.504, respectively, and the AUC of the combination was 0.829 (**Figure 3**; **Table 2B**). Using the DeLong test, we then discovered that the AUC of the combination was significantly higher than that of CEA and CA242 alone (P<0.001, **Figure 3A-D**), but no significant difference was identified between the combination and PNI (P>0.05, **Table 3**).

Establishment of LASSO regression risk model

We employed LASSO regression to assess the factors for early prediction of anastomotic leakage after radical gastrectomy for gastric cancer. The LASSO regression analysis indicated that the history of diabetes and PNI were associated with anastomotic leakage (P<0.05).

Based on this, we opted for lambda.1se (0.05409) for further analysis (**Figure 4A**, **4B**). Utilizing lambda.1se, we devised a risk score formula: 0.493005278 + history of diabetes * 0.018411352 + PNI * (-0.009226992). Relying on the risk scoring formula, we calculated the risk score for each sample. Upon comparing these scores, we noticed that the risk score of the occurrence group was significantly higher than that of the non-occurrence group (P<0.0001, **Figure 4C**). The risk score also demonstrated its potential to predict anastomotic leakage in patients, with an AUC of 0.854 (**Figure 4D**). Additionally, we internally validated the nomogram model using the Bootstrap method (after repeated sampling of raw data 1,000 times). The results showed that the internal verification C-index was 0.863 (0.806-0.920), and the calibration curves fit well to the ideal curve (**Figure 4E**).

Comparison of the combined curve with the regression model curve

At the end of the study, we compared the ROC curve of the combination of PNI, CEA, and CA242 with the ROC curve of the risk model constructed by LASSO regression using the Delong test. The results showed that the AUC of the risk model was significantly greater than the combined curve and PNI (P<0.05, **Table 4**), indicating that the LASSO regression risk model had a higher predictive value for anastomotic leakage in patients.

Discussion

Gastric cancer not only holds a prominent position among common malignant tumors, but also acts as one of the primary catalysts for global cancer mortality [15]. The only curative treatment considered for gastric cancer is surgical resection, which is supplemented by lymph node dissection, including total gastrec-
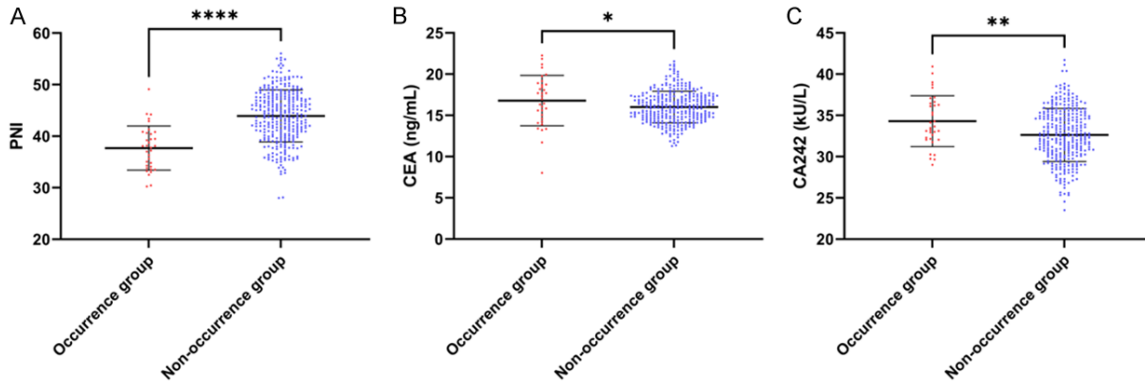
Figure 2. PNI, as well as CEA and CA242 levels on postoperative day 3. A. PNI; B. CEA; C. CA242. Note: PNI, Prognostic Nutritional Index; CEA, Carcinoembryonic Antigen; CA242, Carbohydrate Antigen 242, *P<0.05, **P<0.01, ****P<0.0001.
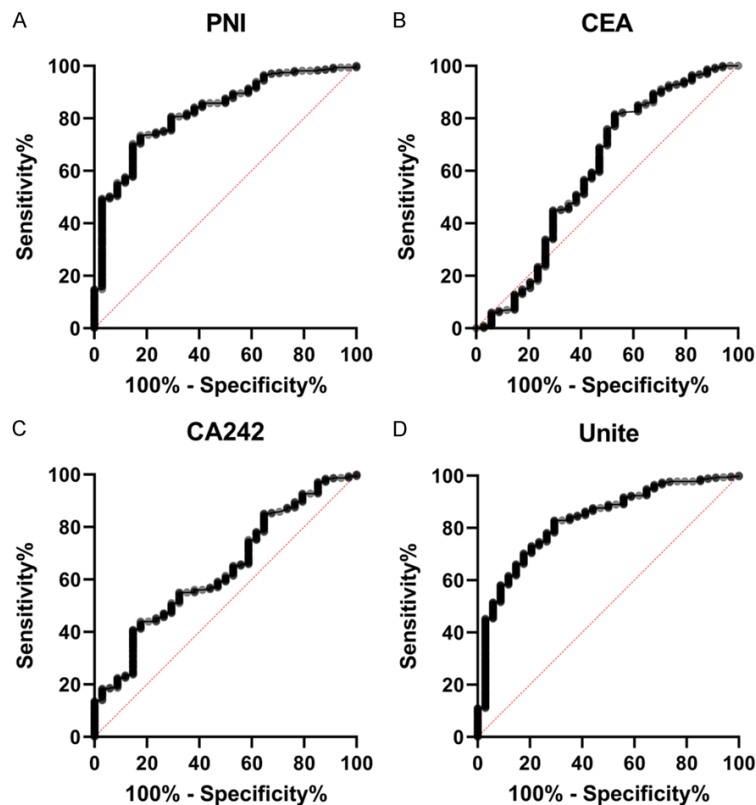

Figure 3. AUC of PNI, CEA, and CA242 for predicting anastomotic leakage. A. AUC of PNI on postoperative day 3; B. AUC of CEA on postoperative day 3; C. AUC of CA242 on postoperative day 3; D. AUC of the combination of the 3 indicators. Note: PNI, Prognostic Nutritional Index; CEA, Carcinoembryonic Antigen; CA242, Carbohydrate Antigen 242; AUC, Area under the curve.

patients afflicted with anastomotic leakage, early detection and prompt treatment can markedly decrease the mortality. The majority of anastomotic leakages manifest within 5 to 7 days after the surgery, and the diagnosis primarily hinges on the patient's clinical manifestations [18]. However, at this juncture, the anastomotic leakage would have already formed, and certain patients' clinical manifestations might not be conspicuous, making it challenging to diagnose the anastomotic leakage solely based on clinical manifestations.

In this investigation, we conducted a retrospective analysis on gastric cancer patients who had undergone radical gastrectomy and D2 lymph node dissection. Previous research conducted by Kim et al. [18] revealed that out of 4916 gastric cancer patients who underwent gastrectomy, 115 patients (equating to 2.3%) developed anastomotic leakage. Another study by Shen et al. [19] reported 34 cases of anastomotic leakage (amounting to 13.13%) in a survey of 259 patients. Our statistics demonstrated an incidence of 9.7% in anastomotic leakage, which aligns with the findings of the above-mentioned research. Through detailed analysis of the clini-

tomy [16], proximal gastrectomy, and distal gastrectomy. Following gastric cancer surgery, there is a risk of anastomotic leakage. Studies [17] have established that postoperative anastomotic leakage is an independent risk factor impacting the prognosis of the patient. For

Table 2B. ROC parameters

Predictive Variable	Area under the curve	Confidence Interval	Cut-off Value	Sensitivity %	Specificity %	Youden's Index
PNI	0.827	0.758-0.895	40.87	73.42%	82.35%	55.77%
CEA	0.601	0.480-0.723	17.65	81.65%	47.06%	28.70%
CA242	0.504	0.380-0.627	38.36	97.15%	23.53%	20.68%
Unite	0.829	0.759-0.898	0.862	82.91%	70.59%	53.50%

Note: ROC, receiver operating characteristic; PNI, Prognostic Nutritional Index; CEA, Carcinoembryonic Antigen; CA242, Carbohydrate Antigen 242.

Table 3. Delong-test

Test Results Comparison	Z value	P value	Area under curve difference	Standard error difference	Confidence Interval	
					lower	upper
PNI-CEA	-5.748	<0.001	-0.428	0.312	-0.574	-0.282
PNI-CA242	-4.879	<0.001	-0.33	0.312	-0.463	-0.198
PNI-Unite	0.134	0.893	0.002	0.261	-0.027	0.031
CEA-CA242	1.355	0.176	0.098	0.350	-0.044	0.239
CEA-Unite	5.164	<0.001	0.430	0.315	0.267	0.593
CA242-Unite	4.383	<0.001	0.332	0.315	0.184	0.481

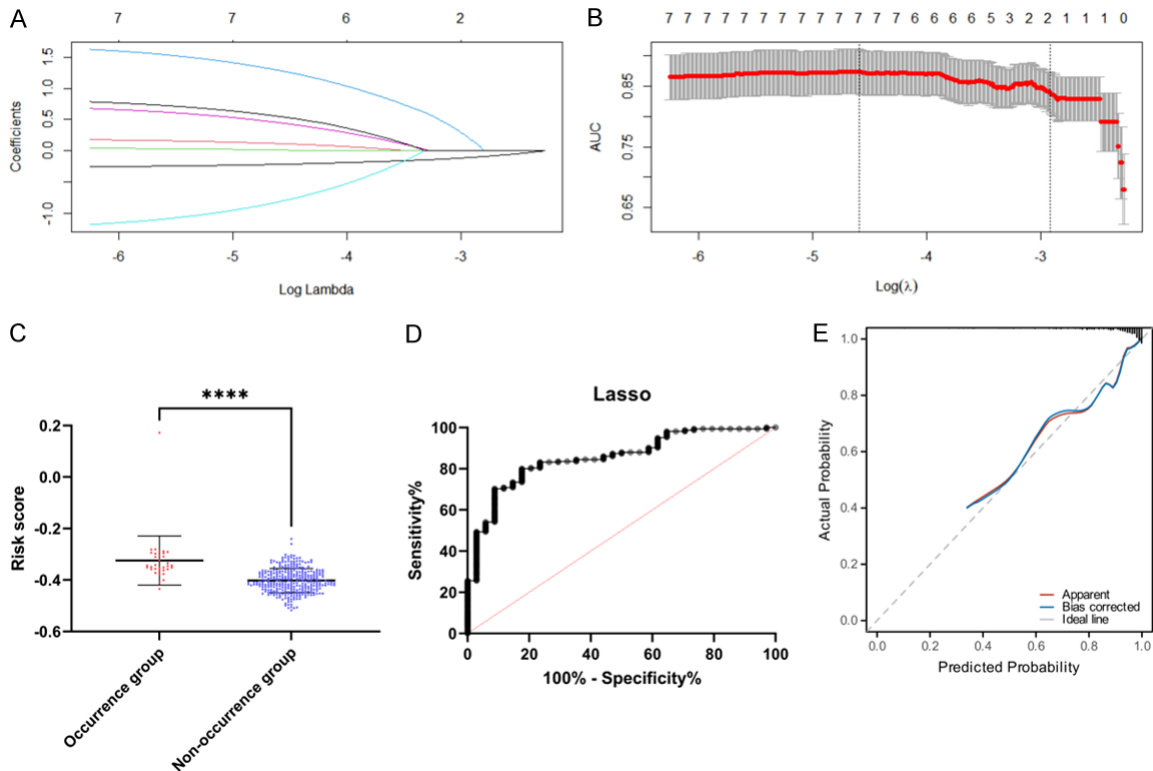Note: PNI, Prognostic Nutritional Index; CEA, Carcinoembryonic Antigen; CA242, Carbohydrate Antigen 242.

Figure 4. Establishment of the LASSO regression risk model. A. Selection of the best lambda in the LASSO model. B. Plot of log(λ) versus error curve. C. Risk model scores for each patient. D. Area under the curve of the risk model in predicting anastomotic leakage in patients. E. Correction curve for predicting anastomotic leakage in patients. Note: LASSO, Least Absolute Shrinkage and Selection Operator, ****P<0.0001.

Table 4. Risk model Delong-test

Test Results Comparison	Z value	P value	Area under curve difference	Standard error difference	Confidence Interval	
					lower	upper
PNI-Risk	10.512	<0.001	0.681	0.260	0.554	0.808
Unite-Risk	10.662	<0.001	0.683	0.261	0.557	0.808

Note: PNI, Prognostic Nutritional Index.

cal and pathological data, it was identified that the percentage of patients suffering from diabetes, manual anastomosis, high TNM staging, and intraoperative bleeding in the occurrence group was noticeably higher than those in the non-occurrence group. This suggests that diabetes, anastomosis method, TNM staging, and intraoperative blood loss were associated with the occurrence of anastomotic leakage in patients with gastric cancer.

In addition, we identified variations in PNI, CEA, and CA242 in patients with anastomotic leakage. Both CEA and CA242 are frequent tumor markers and are extensively utilized for cancer screening and monitoring [20]. These markers can be detected via blood or other biological samples to identify digestive system tumors [21]. This research did not find a direct correlation of CEA and CA242 with anastomotic leakage. It has been discovered that postoperative anastomotic leakage can trigger inflammatory responses and infections, which could potentially impact the levels of CEA and CA242 in the blood [22]. These tumor markers might escalate due to inflammation and infection, but it does not imply that CEA or CA242 itself caused the anastomotic leakage. Prior studies revealed that CEA and CA242 served as prognostic factors for gastric cancer patients, and anastomotic leakage could result in a poor prognosis for the patients [23, 24]. Therefore, there might be an indirect relationship between CEA and CA242 and anastomotic leakage.

To further pinpoint the factors and predictive indicators that influence the anastomosis of gastric cancer patients, we deployed LASSO regression, which is a linear regression analysis method. The primary attribute of LASSO is that it contracts the coefficients of the model during the regression analysis process and can push certain coefficients to zero [25]. This feature makes LASSO regression an effective method for feature selection, allowing us to identify the most crucial predictive variables

[26]. In our regression, we found that diabetes and PNI emerged as predictive factors for anastomotic leakage in gastric cancer patients. At the end of the study, we compared the predictive value of laboratory indicators with the risk model for anastomotic leakage. We discovered that the AUC for PNI predicting anastomotic leakage was substantially larger than that for other single laboratory indicators, and its predictive value was not different from the combination of PNI, CEA, and CA242. This indicates that the detection of CEA and CA242 does not enhance the predictive value of PNI for anastomotic leakage [27]. This also validates that the relationship between CEA and CA242 and anastomotic leakage was indirect. Nonetheless, we discovered that the AUC of the risk model was significantly greater than that of PNI prediction, signifying that the predictive value of the risk model for anastomotic leakage was superior to that of PNI [28].

This study still have its limitations. Firstly, we only recorded the occurrence of anastomotic leakage in patients within one month following surgery, but anastomotic leakage could take place after one month. The short follow-up time resulted in a small sample size in occurrence group, and whether it induces bias in data analysis requires verification. Secondly, as a single-center study, our sample size was limited. If we establish a training set, it could lead to a sharp decline in sample size. Therefore, the generalizability of the model requires more sample data to substantiate.

In conclusion, CEA and CA242 are not promising predictive indicators for anastomotic leakage after gastric cancer surgery, while the predictive model we established can improve the predictive efficiency of anastomotic leakage in gastric cancer patients.

Disclosure of conflict of interest

None.

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