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ORIGINAL RESEARCH

A New Nomogram Based on Early Postoperative NLR for Predicting Infectious Complications After Gastrectomy

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Purpose: Our study aimed to construct a visible model to evaluate the risk of infectious complications after gastrectomy.

Methods: The clinical data of 856 patients who underwent gastrectomy were used to retrieve medical records. Univariate and multivariate analyses were performed to correlate early postoperative NLR and operative variables with postoperative complications, and the construction of the nomogram was based on logistic regression. The concordance index and receiver operating characteristic curves were used to evaluate the model performance.

Results: The postoperative infectious and noninfectious complication rates after gastrectomy were 18.5% (158/856 cases) and 12.3% (105/856 cases) respectively. Postoperative NLR (within 24 h) independently predicted the development of postoperative infectious complication. Multivariate analysis revealed that age, diabetes, body mass index (BMI), intraoperative blood transfusion and postoperative NLR were independent risk factors. The nomogram model showed a good performance in terms of predicting infectious complications after gastrectomy (concordance index=0.718).

Conclusion: Age, diabetes, BMI, intraoperative blood transfusion and postoperative NLR were independent risk factors of postoperative infectious complications after gastrectomy, and a novel nomogram based on these results can be used to predict postoperative infection and has the advantages of simple application and easy access.

Keywords: gastrectomy, infectious complication, nomogram, prediction, risk model

Introduction

Curative gastrectomy remains the most important treatment of gastric malignancies, including total gastrectomy, subtotal gastrectomy, and partial gastrectomy. It is reported that the morbidity of complications after gastrectomy ranges from 17.4% to 37.0%, with the rate of infectious complications between 17.6% and 19.8%.[1–6] Postoperative infectious complications are associated not only with increased length of hospital stay and greater economic cost but also with tumor recurrence and poor prognosis in gastric cancers.[2–5] Therefore, it is important to identify postoperative infectious complications in early stage and take corresponding treatment.

The neutrophil to lymphocyte rate (NLR) is an indicator of systemic inflammatory response, independently predicts poor prognosis after curative resection of several malignant neoplasms, including gastric cancer.[7–10] However, numerous studies have focused on the relationship between the NLR or PLR and tumor characteristics or survival of malignancy; only few evidence suggest that

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preoperative NLR could independently predict postoperative infectious complications in both colorectal cancer and gastric cancer.[2,11] Recently, a link between systemic inflammation and postoperative morbidity was identified by Moyes.[11] However, the relationship between the perioperative systemic inflammatory response and postoperative complications in patients with curative gastrectomy has not been examined and remains uncertain. Therefore, our study aimed to analyze their association and to construct a visible model to evaluate the risk of infectious complications.

Materials and Methods

Patients' Selection

From September 2016 to September 2018, 894 consecutive patients with gastric cancer who underwent gastrectomy at the Department of Gastrointestinal Surgery, the First Affiliated Hospital of Wenzhou Medical University were analyzed retrospectively. According to the exclusion criteria below, 856 patients were eventually enrolled in this study. Curative gastrectomy and lymph node dissection (D1 or D2) were performed according to the guidelines of the Japanese Gastric Cancer Association.[12] All patients had prophylactic use of second-generation cephalosporin for 5 days on average after surgery. Data regarding clinical characteristics, surgery, pathology, and follow-up were retrospectively collected from our database.

Exclusion Criteria

The following patients had been ruled out from this study: (1) Patients who underwent preoperative chemotherapy (6 patients), emergency surgery (16 patients) or R1-R2 resection (7 patients) were excluded; (2) Patients who had evidence of infection or other inflammatory conditions before the surgery were excluded (9 patients).

Blood Analysis

Preoperative blood samples were collected at the first time after admission, while postoperative blood samples were collected within 24 h after surgery, which included hemoglobin, neutrophil, platelet and lymphocyte count, albumin, and tumor markers. The NLR was calculated from the blood sample by dividing the absolute neutrophil count by the absolute lymphocyte count. Similarly, PLR and OPNI were calculated indirectly from the above data.

Determination of NLR Cutoff Value

We determined the optimal discriminator value for NLR by using receiver operating characteristic (ROC) curve analysis. At each value, the sensitivity and specificity for each outcome under study were plotted, generating a ROC curve. The ratio closest to the point with maximum sensitivity and specificity was selected as the cutoff value.

Histological Diagnosis

Resected specimens were examined histopathologically and staged according to the International Union Against Cancer tumor-node-metastasis (TNM) classification.[13] No patient had clinical evidence of infection or other inflammatory conditions at the time of sampling.

Classification of Postoperative Complications

According to the Clavien-Dindo classification, postoperative complications of grade 2 or higher occurred within 30 days after surgery was recorded.[14] The information of complications was obtained from medical records including medical history, laboratory test and imaging examination. The postoperative complications were divided into two groups: infectious complications and non-infectious complications. Infectious complications mainly included intra-abdominal infection, anastomotic leakage, wound infection, and respiratory infection. Non-infectious complications mainly included intra-luminal bleeding, deep vein thrombosis, surgical gastroparesis syndrome, and bowel obstruction. The methods to diagnose postoperative complications were shown in Table S1. If multiple infectious complications occurred in a single patient, only the primitive or the most severe one was counted in the procedure of statistical analysis.

Definition of Infectious Complications

The criteria used to define postoperative infectious complications were referred to the criteria described previously.[11] That is, (1) Wound infection was defined as superficial or deep infection with the presence of pus that required treatment with anti-microbacterical agents or wound drainage; (2) Intra-abdominal abscess was defined as abdominal fluid collection associated with fever or increased white blood cell count that discharged spontaneously or required surgery or ultrasonographically guided drainage, associating with positive microorganism on

blood or fluid culture; (3) Respiratory tract infection was defined by respiratory symptoms and signs combined fever above 38.5°C and a positive X-ray findings, and requirement of antibiotic treatment; (4) Septicemia was defined by clinical symptoms combined with a positive blood culture.

Statistical Analysis

The Kolmogorov–Smirnov test was used to determine whether the variables obey normal distribution. The Mann–Whitney *U*-test was used to compare the non-normal distributed variables between the infectious complication group and the non-infectious complication group. In order to determine the cutoff points of variables, we plotted the receiver operating characteristic curves and the values with the maximal Youden index. According to the cutoff points, patients were divided into two groups. Univariate analysis was performed with the use of χ^2 test. Based on the result of univariate analysis, a multivariate logistic regression analysis was used to confirm the independent risk factors and calculate the odds ratio and 95% confidence interval of each factor. With the use of the risk factors obtained in the multivariate analysis, the nomogram was plotted to assess the postoperative infectious complication probability. The calibration curve of the prediction model was plotted to compare the predicted and actual probability of postoperative infectious complications. We also calculated the concordance index (C-index) to evaluate the model performance. Receiver operating characteristic (ROC) curve was used to compare the performance of the nomogram and individual indicators.

All the statistical analyses and graphics were performed with IBM SPSS 23.0 (SPSS Inc, Armonk, NY) and RStudio software (version 1.2.1335- 2009-2019; RStudio, Inc.). $P<0.05$ was regarded as statistically significant.

Results

Patients' Characteristics

Among total of 856 patients, 640 patients were male and 216 patients were female. The patients' median age was 65 years, ranging from 58 years to 72 years. The tumor location was antrum in 433 cases (50.6%), body in 267 cases (31.2%), cardia in 131 cases (15.3%) and total stomach in 25 cases (2.9%). The surgical approach was laparoscopy in 301 patients (35.2%), and laparotomy in 555 patients (64.8%) (Table 1).

Table 1 Clinical and Pathological Characteristics

Variables	Patients (%)
Age (years)	65 (58–72)
Sex	
Male	640 (74.8%)
Female	216 (25.2%)
BMI (kg/m^2)	22.39 (20.42–22.45)
Hospital stay (d)	19 (15–24)
Site	
Cardia	131 (15.3%)
Body	267 (31.2%)
Antrum	433 (50.6%)
Total stomach	25 (2.9%)
Pathological type	
Ulcerative	590 (68.9%)
Non-ulcerative	266 (31.1%)
Depth of invasion	
T0/T1/T2	368 (43.0%)
T3/T4	488 (57.0%)
Lymphatic involvement	
N0	406 (47.4%)
N1	130 (15.2%)
N2	151 (17.6%)
N3	169 (19.7%)
TNM	
0/I/II	427 (49.9%)
III/IV	429 (50.1%)
Surgical approach	
Laparoscopic	301 (35.2%)
Laparotomy	555 (64.8%)
Infectious complications	
Yes	158 (18.5%)
No	698 (81.5%)

Nutritional Status and Postoperative Early Blood Routine Index

There was no difference between patients with and without postoperative infectious complications in nutritional status before operation. Furthermore, it turned out there was also no difference in the postoperative early individual indicators such as WBC, lymphocyte count and neutrophil count between each group. However, the unit indicators including NLR and PLR were higher in patients with postoperative infectious complication ($P<0.001$) by comparison with those in patients without infectious complication (Table 2).

Table 2 Blood Routine Index and Nutritional Status, According to Infectious Complication Involvement

Factors	Total(n=856)	ICG(n=158)	NICG(n=698)	P
BMI	22.39(20.42–22.45)	22.77(20.84–25.00)	22.27(20.39–24.30)	0.076
ALB	38.40(35.23–41.10)	37.70(34.68–40.70)	38.50(35.30–41.10)	0.168
Pre-OPNI	46.38(42.35–50.24)	45.38(41.60–49.80)	46.48(42.59–50.36)	0.225
WBC	11.34(9.21–14.23)	10.86(8.97–13.43)	11.45(9.30–14.32)	0.147
Neutrophil count	9.56(7.69–12.31)	9.06(7.39–11.52)	9.65(7.73–12.40)	0.162
Lymphocyte count	0.87(0.67–1.11)	0.87(0.66–1.11)	0.87(0.67–1.11)	0.894
Platelet count	195.00(160.00–249.00)	187.00(157.75–235.25)	197.00(161.00–250.00)	0.159
NLR	11.04(8.37–5.17)	13.40(9.89–18.49)	10.61(8.01–14.52)	<0.001*
PLR	232.16(167.54–320.54)	275.38(182.19–364.22)	222.70(163.60–313.74)	<0.001*

Note: *P<0.05 Statistically significant.
Abbreviations: ICG, infectious complication group; NICG, non-infectious complication group; NLR, neutrophil to lymphocyte rate; PLR, platelet to lymphocyte rate; Pre-OPNI, The Onodera Prognostic Nutritional Index before the operation.

Postoperative Complications

After surgery, 262 patients (30.6%) developed postoperative complications, 158 cases (18.5%) of them were infectious complications, and 105 cases (12.3%) were non-infectious complications. Among infectious complications, the intra-abdominal infection without leakage was the most common infectious complication after gastrectomy (52 cases, 31.1%), followed by respiratory infection (36 cases, 21.6%), wound infection (26 cases, 15.6%), and intra-abdominal infection with leakage (25 cases, 15.0%) (Table 3).

Table 3 Postoperative Complications After Gastrectomy

Complications	Patients (%)
Infectious morbidity	158(18.5%)
No. of infectious complications*	167
Intra-abdominal infection without leakage	52(31.1%)
Respiratory infection	36(21.6%)
Wound infection	26(15.6%)
Intra-abdominal infection with leakage	25(15.0%)
Pancreatic fistula	10(6.0%)
Catheter infection	5(3.0%)
Sepsis	4(2.4%)
Lymphatic fistula	4(2.4%)
Urinary tract infection	3(1.8%)
Septic shock	1(0.6%)
Others	1(0.6%)
Noninfectious morbidity	105(12.3%)
No. of noninfectious complications*	108
Lower limb thrombosis	36(33.3%)
Intra-luminal bleeding	18(16.7%)
Surgical gastroparesis syndrome	15(13.9%)
Arrhythmia and heart failure	9(8.3%)
Pleural effusion	8(7.4%)
Liver dysfunction	5(4.6%)
Small bowel obstruction	3(2.8%)
Pulmonary embolism	3(2.8%)
Anastomotic stricture	2(1.9%)
Renal failure	2(1.9%)
Others	7(6.5%)
Total morbidity	262(30.6%)

Note: *After gastrectomy, 9 patients have two infectious complications, 3 patients have two non-infectious complications, 1 patient had both infectious complications and non-infectious complications.

Univariate and Multivariate Analysis

Univariate analyses were used to examine the variables of the development of postoperative infectious and noninfectious complications. As the results of chi-square: age (χ^2=11.279, P=0.001), BMI (χ^2=3.978, P=0.046), diabetes (χ^2=10.057, P=0.002), preoperative OPNI (χ^2=4.663, P=0.031), depth of invasion (χ^2=4.504, P=0.034), lymphatic invasion (χ^2=11.484, P=0.009), reconstruction method (χ^2=10.110, P=0.018), postoperative NLR (χ^2=26.736, P<0.001), postoperative PLR (χ^2=16.578, P<0.001), laparoscopy (χ^2=3.795, P=0.051), and intraoperative blood transfusion (χ^2=17.424, P<0.001) were significantly different between patients with and without postoperative infectious complications (Table 4). This suggested that these variables were potential independent risk factors. Based on these variables, a multivariate logistic regression analysis was performed. On multivariate analysis, high postoperative NLR (OR=2.194, P<0.001), age (OR=1.529, P=0.037), diabetes (OR=2.429, P=0.002), body mass index (OR=1.599, P=0.042) and intraoperative blood transfusion (OR=2.362, P=0.006) were significantly associated with postoperative infectious complications (Table 5). Taken together, age, diabetes, body mass index (BMI), intraoperative blood transfusion and postoperative NLR were the independent predictive indicators of postoperative infectious complications.

Table 4 Univariate Analysis of the Risk of Postoperative Infectious Complications After Gastrectomy

Factors	ICG	NICG	χ^2 value	*P* value
Sex			0.001	0.979
Male	118	522		
Female	40	176		
Age			11.279	0.001*
≥65	101	343		
<65	57	355		
BMI			3.978	0.046*
≥25	39	125		
<25	113	550		
Diabetes			10.057	0.002*
Yes	25	54		
No	133	644		
Smoke			2.154	0.142
Yes	57	210		
No	101	488		
Preoperative albumin			1.120	0.290
≥35	116	540		
<35	42	158		
Preoperative OPNI			4.663	0.031*
≥44.45	89	457		
<44.45	69	241		
Depth of invasion			4.504	0.034*
T0/T1/T2	56	312		
T3/T4	102	386		
Lymphatic invasion			11.484	0.009*
N0	61	345		
N1	36	94		
N2	32	119		
N3	29	140		
Pathological type			0.044	0.834
Ulcerative	110	480		
Non-ulcerative	48	218		
Reconstruction type			10.110	0.018*
Billroth-I	33	186		
Billroth-II	36	185		
Roux-en-Y	80	261		
Postoperative NLR			26.736	<0.001*
≥10.92	110	327		
<10.92	48	371		
Postoperative PLR			16.578	<0.001*
≥217.09	111	366		
<217.09	47	332		
Laparoscopy			3.795	0.051
Yes	45	256		
No	113	442		
Intraoperative blood transfusion			17.424	<0.001*
Yes	24	39		
No	134	659		
Operation time			1.945	0.163
≥180	110	445		
<180	48	253		
Multivisceral resection			1.772	0.183
Yes	16	49		
No	142	649		

Note: *P<0.05 Statistically significant.

Abbreviations: ICG, infectious complication group; NICG, non-infectious complication group; NLR, neutrophil to lymphocyte rate; PLR, platelet to lymphocyte rate; OPNI, The Onodera Prognostic Nutritional Index.

Table 5 Multivariate Analysis of the Risk of Postoperative Infectious Complications After Gastrectomy

Factors	OR	95% CI	*P**
Age			
<65	1		
≥65	1.529	1.027–2.276	0.037
Body mass index			
<25	1		
≥25	1.599	1.018–2.513	0.042
Diabetes			
No	1		
Yes	2.429	1.377–4.283	0.002
Neutrophil to lymphocyte rate			
<10.92	1		
≥10.92	2.194	1.436–3.533	<0.001
Intraoperative blood transfusion			
No	1		
Yes	2.362	1.284–4.344	0.006

Note: *All values in this column are statistically significant (P<0.05).

Construction of the Nomogram for Infectious Complication

Based on the multivariate analysis above, the values of age, diabetes, BMI, intraoperative blood transfusion and postoperative NLR were assigned a corresponding score; subsequently, a novel nomogram was constructed to predict the infectious complication after gastrectomy (Figure 1). The scores of each subgroup variable were summarized to obtain a total score which matches a corresponding infectious complication risk. The C-index of this model was 0.718 and Calibration

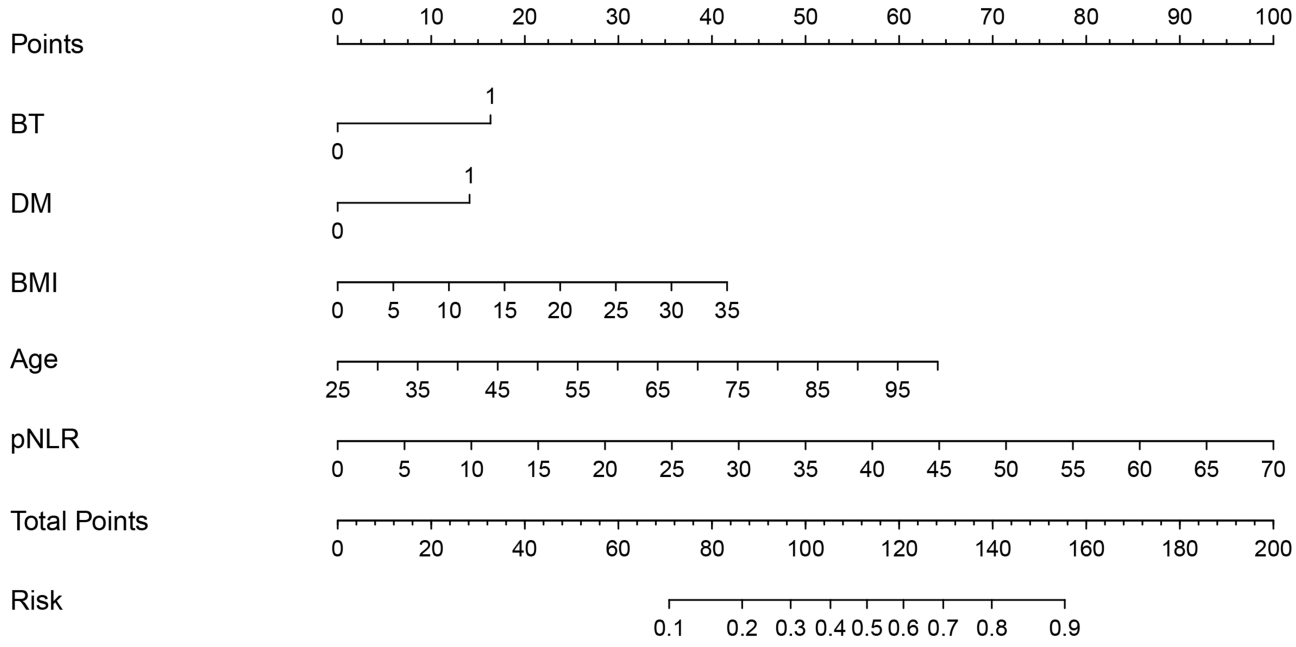

Figure 1 Nomogram for prediction of infectious complications after gastrectomy.
Abbreviations: pNLR, postoperative neutrophil to lymphocyte rate; DM, diabetes; BMI, body mass index; BT, intraoperative blood transfusion.

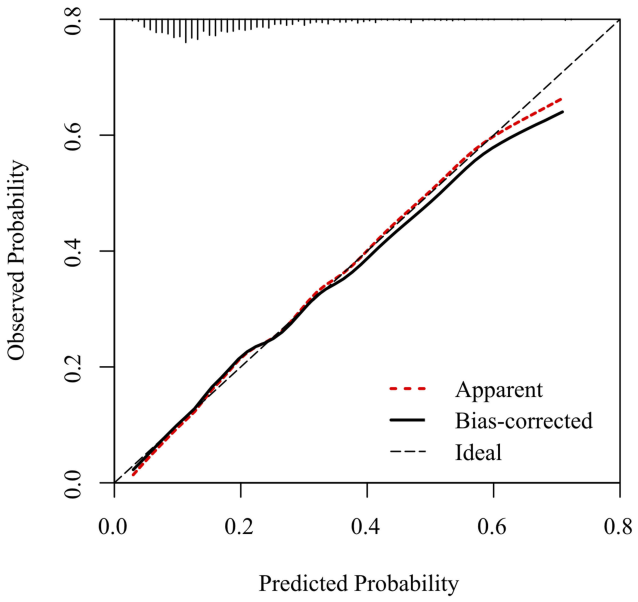

Figure 2 The calibration curve by the nomogram for prediction of infectious complications after gastrectomy. A perfect prediction would correspond to the 45 black dashed line. The red dotted line represents the entire cohort (n=856), and the black solid line is bias-corrected by bootstrapping (B= 1000 repetitions), indicating observed nomogram performance.

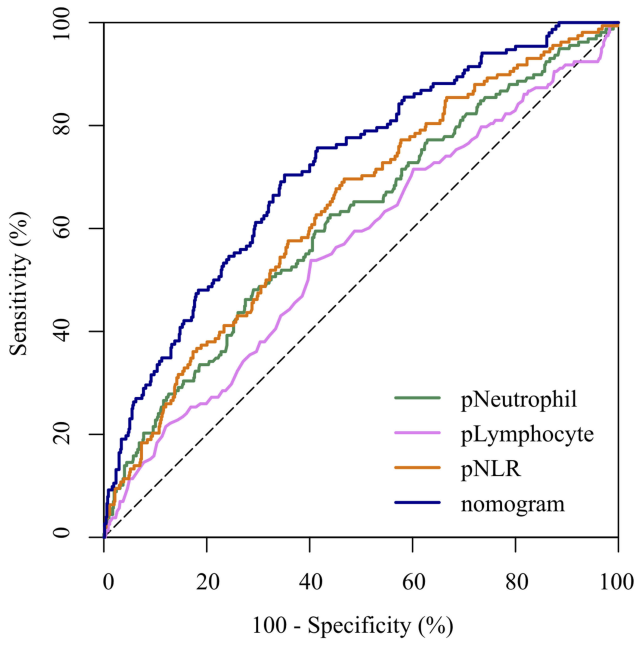

Figure 3 ROC curve of the prognostic nomogram, pNLR, pNeutrophil, and pLymphocyte.
Abbreviations: pNLR, postoperative neutrophil to lymphocyte rate; pNeutrophil, postoperative neutrophil count; pLymphocyte, postoperative lymphocyte count.

was used to verify the performance of the model (Figure 2). To compare the performance of the model with single indicators, we plotted the ROC curve for the nomogram, postoperative NLR, postoperative neutrophil, and postoperative lymphocyte. The area under the ROC curve of these indicators was 0.718 (nomogram), 0.641 (pNLR), 0.615 (pNeutrophil), and 0.562 (pLymphocyte), respectively (Figure 3). Our nomogram showed more reliable discrimination ability as a predictive indicator for infectious complication after gastrectomy.

Discussion

Gastrectomy is still the main treatment for gastric tumors, and it is reported that the morbidity after gastrectomy ranges from 17.4% to 37.0%, including the rate of infectious complications from 17.6% to 19.8%.[1–6] In this study, postoperative complications developed in 262 patients (30.6%) after gastrectomy, including infectious complications of 18.5% (158 patients) and non-infectious complications of 12.3% (105 patients), which is similar to the previous studies.[1–5] The main postoperative infectious complications after gastric operation include intra-abdominal infection, wound infection, anastomosis leakage, and respiratory infection.[1–3] The infectious complications not only increase the length of postoperative hospital stay and financial burden of patients, but also even affect the long-term prognosis of the patient.[2–5] Usually, with the use of antibiotics and local drainage, the treatment of infectious complications can achieve a good therapeutic effect. Therefore, how to identify infectious complications in early stage is of great significance.

Neutrophil to lymphocyte rate (NLR) is an indicator of systemic inflammatory response, and it is very simple to calculate in clinical practice without extra costs. Previous studies have shown that preoperative NLR is correlated with postoperative long-term prognosis of various tumors including gastric cancer, colorectal cancer, hepatic cancer, and breast cancer.[7–10] Evidence suggest that preoperative NLR could independently predict postoperative infectious complications in colorectal cancer and gastric cancer.[2,11] Mohri[2] reported that preoperative NLR was independently associated with the development of postoperative infectious complication after gastrectomy, but not associated with the development of noninfectious complication. In this study, we found that early postoperative NLR (within 24 h) was associated with postoperative infectious complications, and NLR (AUC=0.641) was better than neutrophil (AUC=0.615) in predicting postoperative infectious complications.

The Onodera prognostic nutritional index (OPNI) which was initially presented by Onodera, calculated as 10×serum albumin (g/dl) +0.005×total lymphocyte count, is an indicator of nutritional status.[15] OPNI has been used to assess the outcomes in several cancers in previous studies with promising results, it reported that a low OPNI leads to poorer outcomes.[16–18] However, the correlation between OPNI and short-term outcomes after gastrectomy is not clear. Our study showed that preoperative OPNI was not correlated with the incidence of postoperative infectious complications.

Hamilton[19] reported that major morbidity increased with age, from 16.3% (<65 years old) to 21.5% (76–80 years old), and 24.1% (>80 years old) (P<0.001) after gastrectomy in 3637 patients, driven by higher respiratory and infectious events. Other studies showed the increasing postoperative morbidity rate with age.[6,20,21] In this study, older age was independently associated with increased risk of infectious complication after gastrectomy (OR=1.529, P=0.037). People with diabetes have an increased susceptibility to infection, and diabetes confers an increased risk of developing and dying from an infectious disease.[22] The high blood glucose fluctuation and poor postoperative blood glucose control in diabetic patients were associated with infectious complications after surgery[23,24]; Olsen[25] reported that diabetes was associated with the highest independent risk of spinal surgical site infection. In this study, the incidence of postoperative infectious complications was higher in patients with diabetes than that in patients without diabetes (OR=2.429, P=0.002).

It has been reported that blood transfusion is the risk factor associated with the incidence of postoperative infectious complications after gastrectomy.[26–28] In this study, we found that patients who received intraoperative blood transfusion were more likely to occur postoperative infectious complications (OR =2.362 P =0.006). Xiao[29] analyzed 1835 patients who underwent gastrectomy for gastric cancer, they found BMI≥25 kg/m^2 was the risk factor of postoperative intra-abdominal infection (OR=1.968, 95% CI: 1.107–3.500, P= 0.021). Previous studies also demonstrated that BMI ≥25 kg/m^2 was related to the incidence of surgical site infection (SSI).[28,30] Our results indicated that BMI≥25 kg/m^2 was an independent risk factor of postoperative infectious complications after gastrectomy (OR=1.599, P=0.042).

Studies have shown that there was no significant difference in the overall morbidity of infectious complications after laparoscopic or open gastrectomy.[31,32] In this study, 301 patients (35.2%) underwent laparoscopic surgery, and 555 patients (64.8%) underwent laparotomy. Although the overall morbidity of infectious complication has no difference, laparoscopic surgery means lower local infectious complications (especially wound infection) and shorter hospital stay. On univariate analysis, the postoperative infectious complication rate in laparoscopic surgery patients was lower than that in laparotomy patients (P=0.051). However,

laparoscopy was not an independent risk factor for postoperative infectious complications in multivariate analysis.

Nomogram is a good visual model that combines multiple indicators to predict disease prognosis and has been used in a variety of cancers.[33–36] In this study, age, diabetes, BMI, intraoperative blood transfusion and postoperative NLR were independent risk factors for predicting the postoperative infectious complications after gastrectomy on multivariate analysis. Based on these results, we constructed a nomogram, and it showed more reliable discrimination ability as a predictive indicator for infectious complication after gastrectomy, the C-index of this model was 0.718. To the best of our knowledge, this is the first study to verify the relationship between early postoperative NLR and the infectious complications after gastrectomy. Although our model does not target a specific infectious complication, it has universal significance to predict all infectious complications. In addition, these complications (such as pulmonary infection, incisional infection and intra-abdominal infection) ultimately are needed to be intervened with strong antibiotics. The advantage of our model is that the data is easy to obtain and the risk of infection can be assessed within 24 hrs after the operation. Therefore, the model may be used to alert clinicians to take appropriate measures in reducing the incidence of postoperative infectious complications. When the risk of infection is assessed to be greater than 50%, we recommend prophylactic use of strong antibiotics after surgery (such as third-generation cephalosporin), and better control of blood glucose for diabetes patients. Nevertheless, there are still many deficiencies in this study. Firstly, all patients were from a single-institution, not a multicenter study; Secondly, this was a retrospective study which needs further verification in prospective research.

In conclusion, age, diabetes, BMI, intraoperative blood transfusion and early postoperative NLR were independent risk factors of postoperative infectious complications after gastrectomy, and a novel nomogram based on these results can be used to predict postoperative infection and has the advantages of simple application and easy access.

Ethics Statement

This study was reviewed and approved by the Institutional Review Board (IRB) of The First Affiliated Hospital of Wenzhou Medical University as a retrospective study. This study was conducted in accordance with the Declaration of Helsinki. The requirement for patient-informed consent was waived because of the retrospective nature of this study, and the patients' data confidentiality was protected.

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Author Contributions

All authors contributed to conception and design, acquisition, or analysis of data; participate in drafting and revising the article; gave final approval of the version to be published and agree to be accountable for this work.

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Disclosure

The authors report no conflicts of interest in this work.

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