Cancer Management and Research

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ORIGINAL RESEARCH

The Significance of Fibrinogen in Combination with the Neutrophil to Lymphocyte Ratio in Predicting the Prognosis of Patients with Gastric Cancer

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Objective: To investigate the significance of fibrinogen (Fib) in combination with the neutrophil to lymphocyte ratio (NLR) in predicting the prognosis of patients with gastric cancer.

Methods: The preoperative peripheral blood-related indicators of 281 gastric cancer patients were reviewed retrospectively, and the differences in relationship indicators between the survival and death groups were compared and analyzed. The COX regression analysis and Kaplan–Meier Curve (K-M) were used to assess the prognostic significance of Fib combined with NLR in patients with gastric cancer.

Results: ① The difference between the survival and death groups of patients with gastric cancer was statistically significant in the high and low Fib and NLR levels (X^2=6.868 and 17.051, respectively, all P <0.01).② The correlation between Fib and NLR was remarkable (r=0.266, P=0.000).③ The F-NLR classifications showed statistically significant difference between the survival and death groups for gastric cancer patients (X^2=20.200, P=0.000).④ Except for Fib and the middle/low classification of F-NLR, which was P<0.05, and the rest were all P<0.01. There was a substantial statistical difference between F-NLR classifications, Fib and NLR.⑤ F-NLR was found to be a predictive factor of death in patients with gastric cancer in COX regression analysis (P=0.000).⑥Patients with F-NLR scores of "0", "1" and "2" had 5-year survival rates of 92.6%, 64.0% and 47.2%, respectively, and 3-year survival rates of 92.6%, 74.3% and 51.9%, respectively (all P=0.000).

Conclusion: The combination of Fib and NLR (F-NLR) improves the accuracy of prognosis in patients with gastric cancer.

Keywords: fibrinogen, neutrophil to lymphocyte ratio, F-NLR, gastric cancer, prognosis

Gastric cancer is a common malignant tumor. According to global statistics, its morbidity rate and mortality rate are the 5th and 3rd malignant tumors respectively.[1] Approximately 400,000 new cases of gastric cancer occur each year in China, ranking 2nd in incidence and 3rd in morbidity and mortality of malignant tumors.[2] Despite advances in treatments such as surgery, radiotherapy and targeted therapy, gastric cancer is still the 3rd leading cause of death from malignancy.[3]

Despite the recent development of multimode therapy, the prognosis of gastric cancer has not been greatly improved.[4,5] Many studies have reported a variety of prognostic factors, the most common of which are carcinoma embryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9).[6] Routine detection of serum tumor markers has been widely accepted in the diagnosis and recurrence prediction of gastric cancer. Because of their lack of specificity and sensitivity, these molecular markers cannot be used in the detection of early gastric cancer. Therefore, new and reliable tumor markers are urgently needed.[7] F-NLR has been shown to be an important prognostic marker in several cancers, such as non-small cell lung cancer, esophageal squamous cell carcinoma, and gastric cancer.[8–10] At present, there are still few related research reports, so this

Received: 17 May 2022
Accepted: 23 July 2022
Published: 4 August 2022

study retrospectively analyzed the indicators of peripheral blood of 281 patients with gastric cancer before operation, and then discussed the clinical value of F-NLR in predicting the prognosis of gastric cancer patients.

Materials and Methods

Materials

From April 01, 2011, to July 31, 2020, 519,049 patients were discharged from the hospital, of which 529 patients were diagnosed with gastric cancer by surgical pathology, and 281 patients with gastric cancer with complete information and clear prognosis records. There are 186 males and 95 females, with an average age of 65.6 years, ranging from 28 to 87 years. The exclusion criteria are as follows: ①Severe heart, liver, kidney and other important organ dysfunction.② Complicated with severe infection, diseases of immune system or blood system, etc.③There is a serious mental illness.④Pregnant or Lactating Women.⑤Other malignant tumors. ⑥Non-primary gastric cancer.⑦Preoperative radiotherapy or neoadjuvant chemotherapy. All cases were collected with medical record number, name, gender, age, inpatient department, disease diagnosis, blood transfusion before operation, blood transfusion times, relevant inspection results, follow-up time and prognosis. The last follow-up date is October 31, 2021. The survival time is calculated from the date of operation to death or the last follow-up. All data in this study are preoperative data. All the subjects were operable patients, and there were no advanced stage IV patients.

This research was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Taicang Hospital Affiliated to Soochow University, and informed consent was signed with relevant personnel. We confirm that this data is either anonymous or confidential.

Research Methods

According to the case data of inpatients discharged from the hospital from April 01, 2011, to July 31, 2020, provided by the hospital, all relevant medical records are accessed through the hospital medical record center, and blood coagulation-related indicators such as fibrinogen (Fib) and clinical laboratory data results such as hemoglobin (Hb), white blood cells (WBC), neutrophils (NE), lymphocytes (LY) and monocytes (MO) are obtained. There are no advanced stage IV patients in this group, so the stage is no longer used as an evaluation index.

Grouping Methods

Patients were divided into the death group (including deterioration and death, a total of 47 cases) and the survival group (all cases except for deterioration and death, a total of 234 cases) for comparative analysis.

Taking the death group as the state variable, the ROC curve was drawn, and the area under the curve was 0.647, as shown in Figure 1. According to the curve graph, NLR=1.82 was selected as the best cut-off point. At this time, the corresponding Youden index was the largest, with the corresponding sensitivity of 93.6% and the specificity of 36.9%. Based on this, 281 gastric cancer patients were divided into high NLR level (>1.82) and low NLR level (≤1.82). Palaj et al found that fibrinogen level higher than 3.5g/L was significantly related to poor overall survival rate in gastric cancer patients.[11] Yamamoto et al found that the RFS and OS of the high fibrinogen level were significantly lower than those of the normal fibrinogen level in gastric cancer patients, with a cutoff value of 3.5 g/L.[12] Referring to the above references, we took the value of 3.5g/L as the cut-off value, and divided the patients into high Fib level (>3.5g/L) and low Fib level (≤3.5g/L).

Patients were divided into three F-NLR scoring classifications. High Fib (>3.5g/L) and high NLR (>1.82), with a score of 2, were the high F-NLR classification. High Fib (>3.5g/L) or high NLR (>1.82), with a score of 1, was the middle F-NLR classification. If there was no abnormality, the score was 0, which was the low F-NLR classification.

Statistical Analysis

SPSS 23.0 software was used for statistical analysis. ROC was used to compare the sensitivity and specificity of NLR levels for predicting prognosis. Chi-square test was used to compare the counting data. T-test, F-test and H-test were used to compare the measurement data. The correlation was analyzed by Pearson. SNK-q test was used to compare the mean

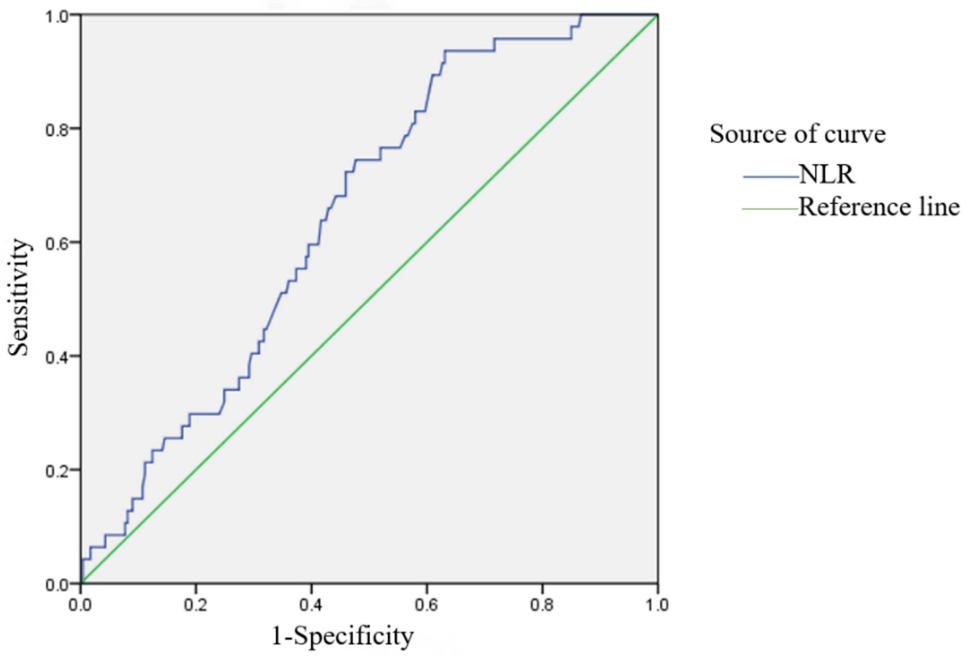

Figure 1 Receiver operating curve for predicting the prognosis with neutrophil to lymphocyte ratio.

between groups. Cox proportional hazard regression model was used to evaluate the prognostic factors, and Kaplan–Meier method was used to draw the survival curve. $P<0.05$ was regarded as a statistically significant difference.

Results

The Relationship Between Fib, NLR and Clinical Characteristics and Hematology

The specific results are shown in Table 1.

As can be seen from Table 1, the high and low Fib levels of different groups, age, preoperative bleeding, blood transfusion, NLR, Fib, Hb, WBC, NE, MO, platelet (PLT), C-reactive protein (CRP), albumin (ALB), C-reactive protein/albumin ratio (CAR), prealbumin (PA) and C-reactive protein to prealbumin ratio (CPR) were statistically significant. Comparative analysis of specific hematological indicators in high and low Fib levels revealed that the values of Hb, ALB and PA in low level Fib were significantly higher than those in high level Fib, while the values of NLR, Fib, WBC, NE, MO, PLT, CRP, CAR and CPR in low level Fib were significantly lower than those in high level Fib. The other indicators, including gender and lymphocyte (LY), were not statistically significant.

It can also be seen from Table 1 that the high and low NLR levels of different groups, gender, NLR, Fib, WBC, NE, LY, MO, CRP, CAR and CPR were statistically significant. Comparative analysis of specific hematological indicators between high and low levels of NLR in patients with gastric cancer revealed that the LY value of low NLR level was significantly higher than that of high NLR level, while the values of NLR, Fib, WBC, NE, MO, CRP, CAR and CPR in low NLR level were significantly lower than those in high NLR level. There was no statistical significance in other indicators including age, preoperative bleeding, blood transfusion, Hb, PLT, ALB and PA.

Results of Correlation Analysis

As seen above, Fib, NLR and related indicators have statistical differences. The analysis results of Fib, NLR and Hb, WBC, PLT, CRP, ALB and PA are shown in Table 2.

The Relationship Between F-NLR and Clinical Characteristics and Hematology

The specific results are shown in Table 3.

Table 1 Comparison of Various Indicators Between the High and Low Fib, NLR Levels

Project		Low Fib	High Fib	χ^2/t	*P*	Low NLR	High NLR	χ^2/t	*P*
n		210	71			90	191		
Group	Survival	182	52	6.868	0.009	87	147	17.051	0.000
	Death	28	19			3	44		
Gender	Male	140	46	0.084	0.772	45	141	15.513	0.000
	Female	70	25			45	50		
Age	>60	140	61	9.654	0.002	62	139	0.454	0.501
	≤60	70	10			28	52		
Preoperative bleeding	Yes	50	28	6.462	0.011	21	57	1.293	0.256
	No	160	43			69	134		
Blood transfusion	Yes	24	16	5.361	0.021	8	32	3.100	0.078
	No	186	55			82	159		
NLR		2.91±2.08	4.56±5.32	2.539	0.013	1.42±0.29	4.21±3.64	10.489	0.000
Fib(g/L)		2.69±0.46	4.16±0.47	22.531	0.000	2.77±0.63	3.17±0.81	4.380	0.000
Hb(g/L)		126.01±21.95	115.34±18.66	3.669	0.000	122.50±17.85	123.69±23.25	0.472	0.637
WBC(x10^9/L)		5.65±1.79	6.80±2.83	3.227	0.002	4.74±1.34	6.50±2.24	8.196	0.000
NE(x10^9/L)		3.69±1.66	4.88±2.80	3.357	0.001	2.49±0.79	4.69±2.10	12.711	0.000
LY(x10^9/L)		1.47±0.53	1.40±0.51	1.020	0.309	1.79±0.56	1.30±0.43	7.431	0.000
MO(x10^9/L)		0.37±0.17	0.46±0.24	3.767	0.000	0.33±0.15	0.42±0.20	4.315	0.000
PLT(x10^9/L)		212.40±70.05	242.61±94.67	2.470	0.015	212.29±59.51	223.68±85.17	1.295	0.196
CRP(mg/L)		3.52±5.49	15.69±23.92	4.249	0.000	2.93±3.86	8.32±16.40	4.293	0.000
ALB(g/L)		39.42±5.23	36.91±4.85	3.563	0.000	38.51±6.18	38.92±4.75	0.610	0.542
CAR		0.10±0.16	0.46±0.74	4.074	0.000	0.09±0.15	0.23±0.50	3.680	0.000
PA(mg/L)		223.26±66.22	169.57±66.65	5.816	0.000	213.25±64.54	208.05±72.88	0.574	0.567
CPR		0.02±0.07	0.17±0.36	3.272	0.002	0.02±0.04	0.08±0.24	3.172	0.002

Abbreviations: NLR, neutrophil to lymphocyte ratio; Fib, fibrinogen; Hb, hemoglobin; WBC, white blood cells; NE, neutrophils; LY, lymphocytes; MO, monocytes; PLT, platelet; CRP, C-reactive protein; ALB, albumin; CAR, C-reactive protein to albumin ratio; PA, prealbumin; CPR, C-reactive protein to prealbumin ratio.

It can be seen from Table 3 that the F-NLR (0, 1, 2) classifications with different groups, gender, age, preoperative bleeding, blood transfusion, Fib, NLR, WBC, Hb, CRP, ALB, CAR, PA and CPR were statistically significant.

After F and H-tests, all the above-mentioned sample averages were statistically significant, except PLT. The SNK-q test was used to compare the means between classifications, and the specific results are shown in Table 4.

It can be seen from Table 4 that the values of Fib, NLR and WBC were different among three classifications. There were differences in CRP, CAR, PA and CPR between high classification and low classification, and between high classification and middle classification. But there was no difference between middle classification and low classification and above-mentioned indicators. There were differences in Hb and ALB between high classification and middle classification, but there was no difference between high classification and low classification, and between middle classification and low classification.

Table 2 Correlation Between Fib, NLR and Other Indicators

Compare Items	*r*	*P*	Compare Items	*r*	*P*
Fib/WBC	0.285	0.000	NLR/WBC	0.649	0.000
Fib/NE	0.305	0.000	NLR/NE	0.798	0.000
Fib/LY	−0.092	0.129	NLR/LY	−0.484	0.000
Fib/MO	0.239	0.000	NLR/MO	0.204	0.001
Fib/NLR	0.266	0.000	NLR/Fib	0.266	0.000
Fib/Hb	−0.234	0.000	NLR/Hb	−0.111	0.064
Fib/PLT	0.209	0.001	NLR/PLT	0.205	0.001
Fib/CRP	0.437	0.000	NLR/CRP	0.351	0.000
Fib/ALB	−0.257	0.000	NLR/ALB	−0.216	0.000
Fib/CAR	0.422	0.000	NLR/CAR	0.395	0.000
Fib/PA	−0.341	0.000	NLR/PA	−0.230	0.000
Fib/CPR	0.413	0.000	NLR/CPR	0.658	0.000

Cox Regression Analysis Results of Various Indicators

The specific results are shown in Table 5.

F-NLR and Survival Curve Analysis

The survival rates of patients were calculated by the Kaplan–Meier method, and the specific results are shown in Figure 2.

It was found that the 5-year survival rates of patients with F-NLR scores of "0", "1" and "2" were 92.6%, 64.0% and 47.2%, respectively (P=0.000). The 3-year survival rates were 92.6%, 74.3% and 51.9%, respectively (P=0.000). In the patients with F-NLR scores of "0" and "1", the median survival time could not be obtained due to the fact that the median time of the statistics had not yet arrived. Only the median survival time of patients in score "2" was 52 months (P=0.000).

Discussion

Studies have shown that NLR and Fib are significantly related to the prognosis of gastric cancer, and can be used as potential indicators of the prognosis of gastric cancer patients.

Inflammatory response and immune status play an important role in the occurrence and development of tumors. NLR, as an indicator reflecting systemic inflammatory response and immune status, was one of the independent risk factors for predicting the prognosis of gastric cancer, colorectal cancer, lung cancer, kidney cancer, breast cancer, cholangiocarcinoma and other malignant tumors.[13] NLR could reflect the relative balance of neutrophils and lymphocytes in tumor microenvironment, and the increase of NLR indicated the change of tumor microenvironment.[14] There was a correlation between preoperative high NLR and high lymph node metastasis in patients with gastric cancer,[15] and the incidence of lymph node metastasis in gastric cancer patients was higher than that in normal patients.[16] Patients in the high NLR level were in a state of high inflammatory reaction, with low individual immunity and decreased antitumor immune function, suggesting a poor prognosis.[17,18] Our results also showed that NLR was an independent prognostic factor for gastric cancer patients (P=0.004). However, we found that the high and low NLR levels had no obvious relationship with age, preoperative bleeding, blood transfusion, Hb, ALB, PA and other indicators, suggesting that NLR could not fully reflect the clinical and hematological characteristics of gastric cancer patients, so it might not have a certain influence on the prognosis.

Table 3 Comparison of Various Indicators Among the Three Classifications of F-NLR (0, 1, 2)

		Low F-NLR (=0 Score)	Middle F-NLR (=1 Score)	High F-NLR (=2 Score)	χ^2/F	*P*
n		76	148	57		
Group	Survival	73	123	38	20.200	
	Death	3	25	19		0.000
Gender	Male	39	107	40	10.385	
	Female	37	41	17		0.006
Age	>60	50	102	49	7.557	
	≤60	26	46	8		0.023
Preoperative bleeding	Yes	16	39	23	6.358	
	No	60	109	34		0.042
Blood transfusion	Yes	6	20	14	7.544	
	No	70	128	43		0.023
Fib(g/L)		2.60±0.45	2.84±0.55	4.20±0.49	177.709	0.000
NLR		1.42±0.29	3.55±2.19	5.27±5.66	*H*=150.883	0.000
WBC(x10^9/L)		4.71±1.39	6.06±1.77	7.27±2.94	*H*=50.504	0.000
Hb(g/L)		124.08±17.96	125.85±23.51	115.68±19.55	*H*=9.123	0.010
PLT(x10^9/L)		209.33±57.80	215.49±75.45	246.11±100.31	*H*=5.087	0.079
CRP(mg/L)		2.71±3.91	3.99±5.96	18.52±25.91	*H*=49.248	0.000
ALB(g/L)		38.52±6.52	39.80±4.25	36.53±5.00	8.574	0.000
CAR		0.08±0.16	0.10±0.16	0.54±0.80	*H*=47.170	0.000
PA(mg/L)		217.25±64.53	223.33±67.32	163.90±67.03	16.546	0.000
CPR		0.02±0.04	0.03±0.07	0.20±0.40	*H*=48.502	0.000

Note: Non-normal distribution data, using rank sum test (*H*).

Table 4 *SNK-q* Test Between Classifications

	High/Low *q*	High/Middle *q*	Middle/Low *q*
Fib	25.13**	24.01**	4.68*
NLR	10.34**	5.19**	7.10**
WBC	10.45**	5.55**	6.84**
Hb	3.17	4.32*	0.83
CRP	10.15**	10.48**	1.02
ALB	3.14	5.81**	2.51
CAR	9.59**	10.31**	0.52
PA	6.47**	8.11**	0.92
CPR	7.77**	8.24**	0.54

Notes: *P<0.05, **P<0.01, the rest are P>0.05.

Table 5 Univariate and Multivariate Analyses in Predicting the Prognosis of Patients with Gastric Cancer

Variables	Categories	Univariate Analysis		Multivariate Analysis	
		HR(95% CI)	*P*	HR(95% CI)	*P*
Gender	Male	1.210(0.654–2.237)	0.544		
Age	>60	1.711(0.850–3.444)	0.132		
Preoperative bleeding	Yes	1.818(1.008–3.278)	0.047*	1.808(0.968–3.377)	0.063
Blood transfusion	Yes	2.000(1.018–3.932)	0.044*	1.309(0.645–2.657)	0.455
Fib(g/L)	>3.5	2.274(1.269–4.074)	0.006**	1.032(0.514–2.075)	0.929
NLR	>1.82	7.728(2.399–24.898)	0.001**	6.090(1.790–20.716)	0.004**
WBC(x10^9/L)	>5.95	1.985(1.116–3.529)	0.020*	1.301(0.702–2.411)	0.403
Hb(g/L)	>152.5	1.263(0.536–2.980)	0.593		
PLT(x10^9/L)	>222.5	2.799(1.553–5.042)	0.001**	2.528(1.368–4.673)	0.003**
CRP(mg/L)	>6.5	3.586(1.964–6.544)	0.000**	2.002(0.686–5.847)	0.204
ALB(g/L)	>17.25	20.271(0.000–1.076E+18)	0.878		
CAR	>0.06	1.983(1.112–3.538)	0.020*	0.903(0.342–2.381)	0.836
PA(mg/L)	>65.55	1.681(0.231–12.209)	0.608		
CPR	>0.02	2.230(1.256–3.958)	0.006**	1.386(0.411–4.669)	0.598
F-NLR	(0.1.2)	2.751(1.763–4.293)	0.000**		

Notes: *P<0.05, **P<0.01. F-NLR is a three-class classification and the result of univariate analysis.

The preoperative Fib level could predict the prognosis of patients with gastric cancer to a certain extent, and it was expected to provide further diagnosis and treatment directions for patients who had undergone surgery and chemotherapy.[19] We found that Fib had obvious correlation with age, preoperative bleeding, blood transfusion, as well

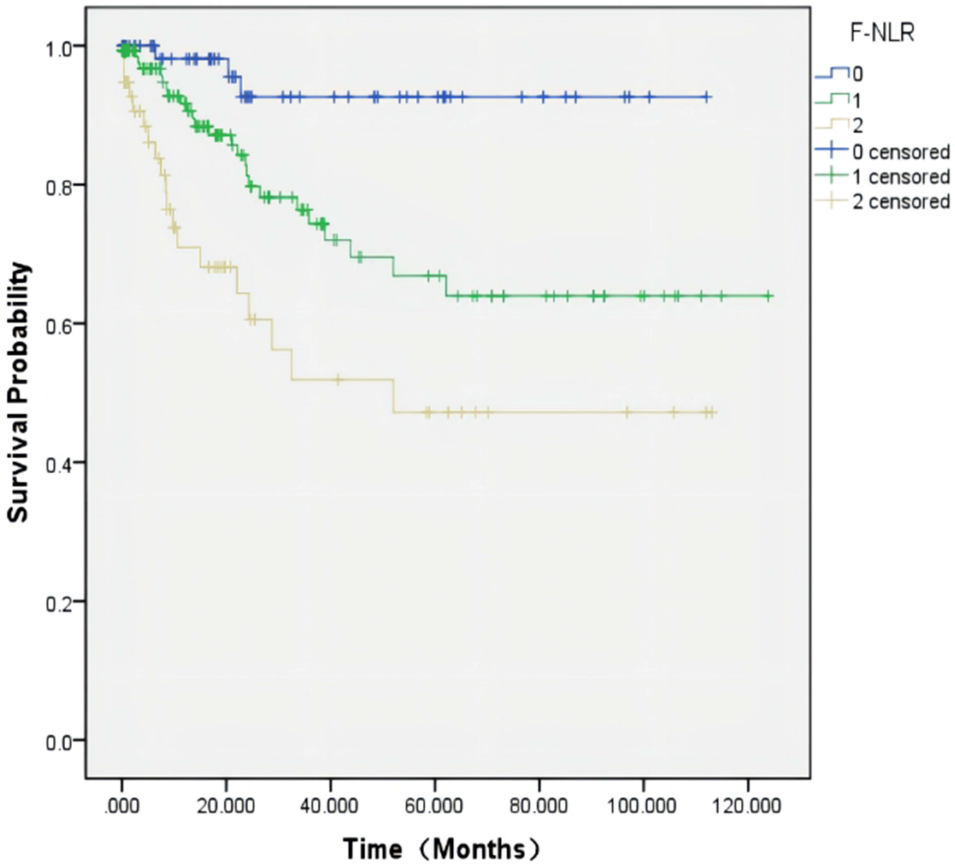

Figure 2 Kaplan–Meier curve for overall survival in gastric cancer patients of F-NLR classifications.

as Hb, WBC, ALB, PA, CAR and CPR in addition to gender, indicating that Fib had great significance in judging the prognosis of patients with gastric cancer. Our results showed that Fib was significant in univariate analysis, but not in multivariate analysis. This may be related to our limited sample size. However, other studies have shown that Fib is an independent factor affecting the prognosis. For example, Yu et al[20] showed that Fib was positively correlated with the progression and metastasis of gastric cancer, and Fib was an independent risk factor, which could be used to predict the survival of gastric cancer patients.

Recently, F-NLR has been used as a new indicator to explore its relationship with tumor prognosis. Huang et al[8] confirmed that the preoperative F-NLR score was a valuable prognostic indicator for patients with early-stage resectable non-small cell lung cancer. Kijima et al[9] reported that the F-NLR score was expected to be a predictor of the efficacy and prognosis of patients with advanced esophageal squamous cell carcinoma undergoing esophagectomy. Liu et al[10] demonstrated that the F-NLR score independently predicted the prognosis of patients undergoing radical gastric cancer surgery. Yamamoto et al[6] pointed out that the prognosis of patients with high F-NLR score may be worse than those with relatively low F-NLR score. F-NLR could increase the adverse effects of Fib or NLR alone, and finally increased its application in predicting tumor progression.[21] We analyzed the relationship between F-NLR and clinical and hematological indicators of gastric cancer patients, and found that in addition to PLT, there were significant correlations with gender, age, preoperative bleeding, blood transfusion and prognosis, as well as Hb, WBC, ALB, PA, CAR, CPR and other indicators. F-NLR can be used as a good indicator to judge the prognosis of gastric cancer patients.

Further analysis showed that the difference between the survival and death groups of gastric cancer patients was statistically significant with F-NLR classifications (X^2=20.200, P=0.000). F-NLR was a prognostic factor of death in patients with gastric cancer (P=0.000). The 5-year survival rates of patients with F-NLR scores of "0", "1" and "2" were 92.6%, 64.0% and 47.2% respectively, and the 3-year survival rates were 92.6%, 74.3% and 51.9% respectively, all of which had a P value of 0.000, suggesting that F-NLR was significantly related to the patient survival rate. According to the above relationship between F-NLR and clinical features and hematology, as well as the results of prognosis analysis, it was showed that F-NLR could effectively judge the prognosis of gastric cancer.

In conclusion, F-NLR is related to the prognosis of gastric cancer patients, and may provide an important reference for the early diagnosis and treatment of cancer patients. Since the cut-off values set by NLR for predicting prognosis are different in different tumors, even in the same tumor, the cut-off value of NLR as an indicator for predicting the prognosis of gastric cancer patients remains to be further explored.[22–28]

Our study also has potential limitations. It is a retrospective analysis with a limited sample size, and this study does not include advanced patients. The results may be biased. We will unify the diagnostic criteria and parameter indicators, strict the inclusion and exclusion criteria of patients, and expand the number of cases in combination with multi-center to further clarify the significance of fibrinogen combined with neutrophil to lymphocyte ratio (F-NLR) on the prognosis of patients with gastric cancer.

Disclosure

The authors report no conflicts of interest in this work.

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