Prognostic significance of preoperative NLR, PLR and LMR in patients suffering from gastric neuroendocrine tumor

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Research

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Abstract

Background: The prognostic value of inflammatory response makers for predicting clinical outcome have been proved valid in various cancers.The aim of this study was to explore the influence of the neutrophil-to-lymphocyte ratio(NLR),platelet-to-lymphocyte ratio(PLR)and lymphocyte-to-monocyte ratio(LMR) on the prognosis of gastric neuroendocrine tumor.

Methods: One hundred and three patients who underwent curative surgery for gastric neuroendocrine tumor were enrolled form 2009-2018 in The first affiliated hospital of Anhui Medical University.NLR,PLR and LMR were calculated from peripheral blood cell counts taken before surgery.Optimal cutoff values of NLR,PLR and LMR were determined on the basis of receiver operating characteristic curve analysis,and their prognostic values were assessed using Kaplan-Meier curve,univariate and multivariate COX regression models.

Result:The cutoff value of NLR,PLR and LMR was 2.08,147.5 and 3.94,respectively.Elevated NLR,PLR and declined LMR were found to relate with diminished Overall survival (OS) in surgical gNET patients.Multivariate analysis identified the LMR(HR=0.923 (0.860-0.991), P=0.027);tumor size(HR=1.130 (1.032-1.239),P = 0.009) and high grade postoperative complication(HR=2.847 (1.129-7.480), P =0.027) as independent prognostic factors.

Conclusion: Inflammatory response markers can predict clinical outcome in patients with gNET,especially LMR might be considered as a convenient indicator for patients' prognosis

Synopsis

Through the analysis of the data of 103 patients with gNET, we determined the predictive significance of the preoperative inflammatory indicators NLR, PLR and LMR on the patient's short-term and long-term results, which will help the clinical diagnosis and treatment of gNET patients in the future.

Introduction

Gastric neuroendocrine tumors (gNETs) are neoplasms derived from the enterocharomaffin -like cells (ECL cells) of the gastric mucosa .They are rare lesions with an indolent behavior and neuroendocrine differentiatio(1). A recent independent analysis of the SEER database also found that the incidence of gastrointestinal NETs increased from 1975 to 2008(2). The reasons for this increase are unclear, although it seems likely that improved diagnosis

and classification is a factor(3).gastric NETs consist of a complex disease that includes different subtypes with distinct management and prognosis.Surgery is still the mainstay for the treatment of local or locoregional gNETs .Patients with gNETs that are symptomatic intermediate -to-high grade,or measure greater than 2cm are recommended to undergo formal oncological surgery,and the surgical approach for gNETs primarily depends on tumor location(4).

In recent years ,thanks to a higher early diagnosis rate and a wider range of treatment options ,the Overall survival rate of patients with NETs has increased to a certain extent than before.However ,a clearer understanding of prognosis factors for OS in patients with gNETs may therefore facilitate the implementation of treatment guidelines recommending the individualiazation of therapy(3).

According to our best knowledge of the literature ,inflammation is regarded as a pivotal driver for the development and progression of cancer.The neutrophil-to-lymphocyte ratio (NLR); lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) can reflect the state of tumor microenvironment composed of inflammatory factors and inflammatory cells ,and can be used to assess the degree of systematic inflammation (5–7).

Studies have proved that systematic inflammatory indicators can be used as a reliable predict tools to guide the clinical prognosis in several cancers.Preoperative NLR,PLR and LMR have been shown to be related to prognosis in a variety of cancer including :colorectal cancer ,esophagus cancer ,ovarian cancer ,lung cancer, biliary tract cancer,osteosarcoma.etc(8–13).

The aim of our study was to analyse the prognostic impact of preoperative NLR,PLR and LMR in patients with gNETs.We hypothesis that elevated NLR,PLR and declined LMR are associated with unfavorable outcomes in gNETs .

Methods

Patients and samples

A total of 103 patients who were diagnosed with gNET and underwent radical surgery at the First Affiliated Hospital of Anhui Medical University between January 2009 and August 2018 were enrolled and followed up until December 2020.The inclusion criteria are as follows :

(1) No preoperative radiotherapy, chemotherapy, immunotherapy, molecular targeted therapy, etc.;

(2) No other tumors, no history of other malignant tumors;

(3) No history of upper abdominal surgery, and suffered radical resection of gastric cancer this time

(4) No history of immune disease before operation, no other serious diseases such as acute coronary heart disease, liver cirrhosis, chronic kidney disease, chronic blood system disease, etc. No recent infection evidence;

(5) Postoperative pathological diagnosis of gastric neuroendocrine Cancer or gastric mixed neuroendocrine carcinoma;

(6) Postoperative pathological data is complete, and follow-up information is complete.

All gNET patients were confirmed in accordance with histological evidence ,or patients without histological confirmation were excluded from the present study .This study was approved by the institution ethics commission of Anhui Medical University ,and written informed consents were obtained from all participants.The pathological staging of all patients was based on the 8th edition of UICC/AJCC TNM staging .

Clinical-pathological and laboratory data

The clinical -pathological data were collected from medical records at the Department of Hospital Medical Record .The laboratory data (white cell ,neutrophil ,lymphocyte ,monocyte and platelet counts ,AFP,CEA,CA125,CA153,CA72-4.etc) were collected from blood routine test with each patient blood sample obtained from 7 to 9am before surgical operation which was detected by Sysmex XT-1800i Automated Hematology System.

Following -up data

Patients ‘follow -up examinations were performed at regular intervals (every 3 months within the first to third year ,6 months within the fourth to the fifth year).OS were defined as the time from the operation day to the date of death or the end point time of follow-up to December 30.2020.

Statistical analysis

The Receiver Operating Characteristic (ROC) curve was used to assess the sensitivity and specificity for the 5-year OS and the largest Youden’s index was estimated to determine the optimal NLR,PLR and LMR cutoff values(14) .comparison of categorical variables was conducted through chi-square test while the Student’s T test and Mann-Whitney U test were applied to the comparison of continuous variables .Survival curve were plotted by the Kaplan-Meier method and the results acquired from log-rank test were used to judge significance. The significant predictors for OS determined through univariate analysis were evaluated through multivariate analysis using Cox proportion hazards model .All data analyses was completed by SPSS 22.0 software(IBM,USA),and P□0.05 was considered statistically significant .

Results

As it was performed through ROC curve(Fig. 1),the areas under the curve for NLR,PLR and LMR were 0.665(P = 0.021),0.617(P = 0.039),and 0.619(P = 0.035),respectively .The optimal cut-off values were 2.08 for NLR(sensitivity ,48.94%;specificity ,78.57%);147.5 for PLR(sensitivity ,70.21%;specificity ,57.14%)and 3.94 for LMR(sensitivity ,61.7%;specificity ,64.29%).

Effect of preoperative inflammatory indicator(NLR,PLR,LMR) on patients characteristics and perioperative outcomes

All patients were dividend into two groups according to their NLR,PLR and LMR in turn on the basis of the three different optimal cut-off values. After the grouping is completed, we displayed the patient's general background characteristics, tumor-related characteristics, surgery-related characteristics, and post-operative characteristics in the table 1, and the statistical values were calculated .As we can see in the table 1,between the low -and high -NLR groups ,significant discrepancy were observed in preoperative symptoms amount (P = 0.003),tumor size (P = 0.004)

intraoperative blood loss (P = 0.009),intraoperative blood transfusion (P = 0.048),postoperative complications(P = 0.008),length of postoperative hospital stay(P = 0.006);between the low- and high-PLR groups ,significant discrepancy were observed in patients age (P = 0.024), preoperative symptoms amount (P = 0.004),CA72-4 (P = 0.017),vascular invasion (P = 0.009), intraoperative blood loss (P□0.001);and between low- and high -LMR groups,significant discrepancy were observed in No. of lymph node metastasis (P = 0.044).

Survival analysis for gastric neuroendocrine tumor patients

The Median survival time (MST) for all 103 patients was 19months .As it is shown in the survival diagrams(Fig. 2,figure 3□figure 4) ,the patients in the high NLR group ,high PLR group and low LMR group had a worse prognosis than the patients in the low NLR group ,low PLR group and high LMR group.

In addition to NLR,PLR and LMR.The relationship between other prognostic factors and survival time has also been explored ,All patients were divided into two groups according to various prognostic-related indicators .In terms of continuous variables ,the mean value or median is usually selected as the cut-off value while categorical variable can be grouped directly .As it is shown in Table 2,including preoperative NLR(P = 0.006) ,PLR(P = 0.006),LMR(P = 0.006),serum CA153 level (P = 0.049),tumor size (P = 0.011),tumor pathological stage (P = 0.021),high grade postoperative complications(P□0.001) and postoperative hospitalization days(P = 0.035) has showed discrepancy in survival time between groups which is statistically significant .

Multivariate analysis

We can see from table 3,Multivariate analysis revealed that high grade postoperative complications (Hazard ratio [HR], 2.847(1.129–7.480); p = 0.027), large tumor size (HR, 1.130(1.032–1.239); P = 0.009), and low preoperative LMR (HR, 0.923(0.860–0.991); p = 0.027) were strong predictive factors for poor survival,thus to be regarded as independent unfavorable factors for OS.

Discussion

Gastric neuroendocrine tumor is a rare type accounting for a minority of overall gastric cancer ,with an projected prevalence of NETs in the US population in 2014 was 171,321(2) ,it's difficult to diagnosis in early phase because of the complex clinical performance and various biological characteristics of it. The prognosis of patients with such diseases is still not optimistic, although both AJCC and ENETS have published authoritative classification and staging standards(15, 16)

Over the past decades ,more and more evidence confirmed CRI (Cancer -related inflammation) can promote the occurrence and development of tumors ,and help them achieve all characteristic abilities including the ability to evade immune surveillance(17).Now there are studies have shown that neutrophil plays a pivotal role in many stage of tumor progression .It promotes tumor grow through secrete a variety of cytokines such as GMCSF, TNF-α,IL-1,and IL-8(6, 18).Neutrophil infiltration in human tumor is associated with poor prognosis in patients with liver cancer ,cervical cancer and colorectal cancer (19–21).In addition ,lymphocytes play a critical role in tumor-related immune reaction ,several studies have reported that lymphocyte infiltration around tumor is associated with a good response to cytotoxic therapy and better prognosis. Lymphocyte infiltration is common in NET through immunohistochemical evaluation of CD3,CD4,CD8 and CD56(22–24).Studies have shown that platelet may increase angiogenesis and release growth factors to participate in the inflammatory response(25) .Platelets aggregate and degranulate in the tumor microenvironment ,and release platelet -derived growth factors and transforming growth factors to promote tumor cell growth(26) .

NLR,PLR and LMR can be used to reflect the balance of the body's tumor-related inflammatory response and immune response .Previous studies have shown that high NLR,PLR and low LMR usually indicate an unfavorable prognosis for tumor patients .

A study conducted by Gaitanidis et al.on pancreatic neuroendocine tumors found that preoperative NLR2.3 can be regarded as an independent factor in evaluating the prognosis of patients with poor progression-free survival ,regardless of whether the patient has underwent surgery(27).A retrospective analysis contain 1028 patients with gastric cancer by Shimada et al concluded that NLR is an independent risk factor for the reduced survival rate of patients with gastric cancer(28) .A meta-analysis of 2557 pancreatic cancer patients in 10 studies by Hu RJ et al .showed that lower preoperative LMR is associated with worse clinicopathological features and poor prognosis of patients with advanced PC (pancreatic cancer) (29). A retrospective study by Li QG, Li P, Tang D, Chen J, Wang DR. showed that perioperative results, including postoperative complications, intraoperative blood loss and intraoperative blood transfusion, etc., can affect the gastric cancer patients' survival rate after surgery. They believe that postoperative complications lead to a prolonged period of immunosuppression, so that the remaining tumor cells proliferate in the host and continue to survive (30). A study by Kraft A suggested that tumor micrometastasis may develop rapidly in the course of short-term or long-term relative immunosuppression caused by postoperative complications (31). In addition, Nash GF studies have shown that both sepsis and blood transfusion can stimulate the release of vascular endothelial growth factor, which is one of the most effective stimulators for the metastatic growth of tumor cells (32). This is consistent with the results of this study.

In summary, gastric neuroendocrine tumors are relatively rare and highly malignant neuroendocrine tumors. The preoperative systemic inflammatory indicators NLR, PLR and LMR are related to the long-term prognosis and perioperative prognosis of patients with gastric neuroendocrine cancer. We suggest that the preoperative inflammatory indicators NLR, PLR and LMR should be included in the short-term and long-term prognosis evaluation of patients with gastric neuroendocrine cancer. In addition, as far as

the current research is concerned, its limitations are obvious. First of all, dynamic monitoring of NLR ,PLR and LMR throughout the perioperative period will be more effective in predicting gNETs patients ' survival.Furthermore,Since this study is a single-center retrospective study with a relatively small patient cohort, these results will need to be confirmed by other large-scale prospective studies of multiple centers.

Declarations

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Authors' contributions

ZBB designed the research and made corrections and supplements to the main content of the manuscript .FC drafted the manuscript of the research and analyzed the data .All authors read and approved the final manuscript .

Competing interests

The authors declare that they have no competing interests

Consent for publication

Not applicable

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the First Affiliated Hospital of Anhui Medical University, and with the 1964 Declaration of Helsinki and its late amendments or comparable ethical standards

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Tables

Table □ □Comparison of various factors between groups

Factor	NLR		P value	PLR		P value	LMR		P value
	low-NLR Group （n=35）	high-NLR Group （n=68）		low-PLR Group （n=58）	high-PLR Group （n=45）		low-LMR Group （n=54）	high-LMR Group （n=49）	
Patient Characteristics									
Age	66(60-70)	63(59-71.75)	0.464	67(61.5-71.0)	62(58.0-69.0)	0.024*	66(59.75-71.25)	63(59.0-70.50)	0.385
Sex ratio(male:female)	27:8	57:11	0.408	48:10	36:9	0.720	47:7	37:12	0.132
BMI(kg/m2)	21.57±2.572	21.65±3.157	0.910	21.65±2.845	21.59±3.171	0.926	21.52±2.733	21.74±3.272	0.746
ASA score(1-4)	2(2-3)	2(2-2)	0.136	2(2-2.25)	2(2-2)	0.533	2(2-2)	2(2-3)	0.184
Preoperative symptoms amount	3(2-4)	4(3-5)	0.003*	3(2-5)	4(3-5)	0.004*	4(3-5)	3(2-5)	0.160
Loss of weight (kg)	1.0(0-3)	2.0(0.25-5.0)	0.157	1.0(0-3.25)	2.0(1-5.0)	0.128	2.0(1-5)	1.0(0-5)	0.191
CEA(ng/ml)	2.91(1.80-5.65)	2.75(1.57-6.13)	0.981	2.59(1.59-5.46)	3.20(1.95-6.60)	0.395	3.13(1.60-5.86)	2.6(1.80-5.40)	0.548
CA199(U/ml) (normal:abnormal)	33:2	61:7	0.681	52:6	42:3	0.761	49:5	45:4	0.844
CA72-4(U/ml incomplete) (normal:abnormal)	19:1	35:11	0.138	34:3	20:9	0.017*	26:9	28:3	0.092
AFP(ng/ml) (normal:abnormal)	31:4	57:11	0.725	52:6	36:9	0.168	45:9	43:6	0.525
CA125(U/ml incomplete) (normal:abnormal)	31:1	53:7	0.319	48:4	36:4	0.697	45:4	39:4	0.847
CA153(U/ml incomplete)	6.75(5.26-8.16)	6.13(3.48-6.83)	0.074	6.4(4.8-7.86)	5.9(3.76-7.0)	0.208	6.4(5.1-8.2)	5.9(4.2-6.9)	0.187
Tumor-related characteristics									
Tumor location (cardia:others)	29:6	51:17	0.364	48:10	32:13	0.159	38:16	42:7	0.062
Tumot size(cm)	4.0(3.0-6.0)	5.75(4.13-7.15)	0.004*	5.0(3.87-7)	6.0(4.0-7.5)	0.115	5.75(4-7.2)	5.0(3.5-6.5)	0.081
T staging (T2+T3:T4a+T4b)	3:32	4:64	0.920	2:56	5:40	0.255	3:51	4:45	0.599
N staging (N0=0,N1=1,N2=2,N3=3)	2(1-2)	1(0-3)	0.644	2(0-3)	1(0-3)	0.639	2(1-3)	1(0-2)	0.070
M staging (M0:M1)	32:3	61:7	0.780	52:6	41:4	0.804	47:7	46:3	0.242
Pathology Stage (UICC,7th edition) A=1 B=2 A=3 B=4 A=5 B=6 C=7 =8	6(5-7)	6(4-7)	0.788	6 4-7	6 5-7	0.352	6(5-7)	6(4-7)	0.096
NET classification (NEC: MNEC)	22:13	47:21	0.522	39:19	30:15	0.951	37:17	32:17	0.729
NET cell classification (Large :Small)	32:3	60:8	0.873	49:9	43:2	0.138	48:6	44:5	0.882
Nerve invasion	7(20%)	8(11.8%)	0.262	7 12.1%	8 17.8%	0.415	10(18.5%)	5(10.2%)	0.232
Vascular invasion	9(25.7%)	25(36.8%)	0.259	13 22.4%	21 46.7%	0.009*	19(35.2%)	15(30.6%)	0.622
Ki-67 index(incomplete)	60%(50%-65%)	60%(50%-71.25%)	0.772	60% 45%-65%	60% 50%-70%	0.706	60%(47.5%-67.5%)	60%(50%-70%)	0.287
Number of lymph nodes metastases	3(1-6)	2.5(0-9)	0.748	3 0-7	2 0-9.5	0.814	4(1-9)	1(0-5)	0.044*
Number of lymph nodes dissected	16.51±7.233	16.13±6.994	0.796	16.1±6.431	16.5±7.832	0.797	16.72±7.288	15.76±6.802	0.489
Lymph node metastasis rate	26.67% (5%-36.84%)	14.64%(0-43.03%)	0.686	24.26% 0-41.25%	14.28% 0-41.42%	0.859	31.41% (7.14%-45%)	12.5%(0-33.3%)	0.059
Surgical characteristics									
Operative route			0.827			0.708			0.886
Laparotomy	32	63		54	41		50	45	
Laparoscopic surgery	3	5		4	4		4	4	
Excision extentsion			0.571			0.874			0.111
Total gastrectomy	28	51		46	32		38	41	
Distal gastrectomy	2	7		4	5		6	3	
Proximal gastrectomy	1	1		1	1		0	2	
Palliative surgery	4	9		7	6		10	3	
Reconstruction way			0.708			0.639			0.858
Roux-en-Y	32	59		52	39		48	43	
Others	3	9		6	6		6	6	
Operating time(minutes)	184.29±73.895	187.79±62.762	0.811	190.52±75.705	181.56	0.501	186.39±66.591	186.84±66.901	0.973
Combined with other organ excison	8(22.9%)	12(17.6%)	0.527	13 22.4%	7 15.6%	0.383	11(20.4%)	9(18.4%)	0.797
Intraoperative blood loss(ml)	30(20-50)	50(30-150)	0.009*	30 20-50	50 50-150	0.001*	50(20-150)	50(20-50)	0.222
Intraoperative blood transfusion	2(5.7%)	14(20.56%)	0.048*	6 10.3%	10 22.2%	0.099	11(20.4%)	5(10.2%)	0.155
Postoperative characteristics									
Postoperative complications	3(8.6%)	22(32.4%)	0.008*	11 19.0%	14 31.1%	0.154	17(31.5%)	8(16.3%)	0.073
Length of postoperative hospital stay(days)	10(8-12)	11(10-13)	0.006*	11 9-13	10 10-12	0.734	11(10-13)	10(9-12)	0.411
Postoperative anal exhaust time (days)	4.06±0.814	4.10±1.394	0.865	4.11±0.838	4.07±1.601	0.876	4.19±1.480	3.98±0.863	0.387
Postoperative time of getting out of bed(days)	2.68±0.806	3.03±1.728	0.303	2.67±0.852	3.18±2.003	0.085	3.07±1.882	2.69±0.829	0.192
Postoperative recurrence	23(65.7%)	55(80.9%)	0.089	42(72.4%)	36(80%)	0.373	43(79.6%)	35(71.4%)	0.332
Postoperative chemotherapy	17(48.6%)	28(41.2%)	0.474	26(44.8%)	19(42.2%)	0.791	27(50%)	18(36.7%)	0.175

Footnotes NLR,neutrophil -to-lymphocyte ratio ;PLR,platelet -to lymphocyte ratio ;LMR,lympho-

cyte -to- monocyte ratio ;BMI ,body mass index ;ASA,American society of Anesthesiologist;

CEA,carcinoembryonic antigen ;CA19-9, carbohydrate antigen 19-9;CA72-4, carbohydrate antigen 72-4;AFP, α-fetoprotein ;CA 125, carbohydrate antigen 125,CA153, carbohydrate antigen153 UICC, Union for International Cancer Control,;Cardia,the opening into the stomach and that part of the stomach connected to the esophagus ;NEC,neuroendocrine carcinoma ;MNEC,mixed neuroendocrine carcinoma; Ki-67：Proliferating cell related antigen

*:P＜0.05

Table2 Survival analysis of prognostic factors at different index

Parameter	Cut-off value	No.of Patient	MST(month)	P value

Systemic inflammatory response markers

NLR	2.08			0.023*
High		68	13	
Low		35	30	
LMR	3.94			0.006*
High		49	28	
Low		54	13	
Lymphocyte count	1.64			0.117
High		40	27	
Low		63	13	
PLR	147.5			0.012*
High		47	13	
low		56	28	
Cancer-related prognostic factors				
CEA(ng/ml)	4.75			0.592
High		31	22	
Low		72	19	
AFP(ng/ml)	5.0			0.441
High		28	20	
Low		75	18	
CA199(U/ml)	8.01			0.175
High		50	20	
Low		53	19	
CA72-4（incomplete, U/ml）	5.85			0.171
High		33	20	
Low		33	32	
CA125（incomplete, U/ml）	9.74			0.317
High		46	16	
Low		46	28	
CA153（incomplete, U/ml）	6.2			0.049*
High		35	20	
Low		37	28	
Tumor size(cm)	5			0.011*
Large		48	12	
Small		55	28	
Tumor location				0.453
Cardia		80	20	
Others		23	17	
NET classification				0.500
NEC		69	19	
MNEC		34	20	
NET cell classification				0.228
Large		92	20	
Small		11	12	
Lymphnode metastasis				0.096
Yes		74	18	
no		29	27	
Vascular invasion				0.441
Yes		34	15	
No		69	22	
Nerve invasion				0.810
Yes		15	27	
No		88	19	
Stage(UICC 7th.Edition)				0.021*
Ⅰ/Ⅱ		25	32	
Ⅲ/Ⅳ		78	17	
Host-related prognostic factors				
Age	65			0.853
High		54	19	
Low		49	20	
Sex ratio				0.164
Male		84	19	
Female		19	30	
BMI(kg/m^2)	21.3			0.800
High		39	20	
Low		44	20	
ASA score(1-4)	3			0.119
High		20	27	
Low		83	18	

Loss of weight (kg)	2			0.285
High		37	22	
low		66	19	
Preoperative symptoms amount	5			0.367
High				
Low		34	20	
Postoperative chemotherapy		69	19	
Yes				0.698
No		45	20	
		58	19	
Surgery-related prognostic factors				
Operating time (minutes)	180			0.914
High		42	22	
Low		61	16	
Intraoperative blood loss (ml)	50			0.705
High		32	18	
Low		71	20	
Intraoperative blood Transfusion				0.255
Yes				
No		16	28	
Excision extentsion		87	19	
Total gastrectomy				0.059
Others		79	22	
Length of postoperative hospital stay		24	11	
High	10			0.035*
Low				
Postoperative complications (Score≧Clavien-Dindo grade III)		51	12	
high		52	28	
low				<0.001*
		9	10	
		94	20	

Footnotes：NLR,neutrophil -to-lymphocyte ratio ;PLR,platelet -to lymphocyte ratio ;LMR,lymphocyte -to- monocyte ratio ;BMI ,body mass index ;ASA,American society of Anesthesiologist; CEA,carcinoembryonic antigen ;CA19-9, carbohydrate antigen 19-9;CA72-4, carbohydrate antigen 72-4;AFP, α-fetoprotein ;CA 125, carbohydrate antigen 125,CA153, carbohydrate antigen153 UICC, Union for International Cancer Control,;Cardia,the opening into the stomach and that part of the stomach connected to the esophagus ;NEC,neuroendocrine carcinoma ;MNEC,mixed neuroendocrine carcinoma; Clavien-Dindo grade, assesses the grade of postoperative complications； MST：median survival time (month)
*：P＜0.05.

Table ： Univariate & Multivariate regression analyses of prognostic factors

Parameters	Univariate analyses		Multivariate analyses	
	Uncorrected HR & 95% CI	P value	Corrected HR & 95% CI	P value
Age	0.994 (0.972□1.016)	0.585	/	/
Sex				
male	1.470 (0.843□2.564)	0.174	/	/
female	1			
Excision extentsion				
others	1.571 (0.970□2.545)	0.066	1.314 (0.676□2.555)	0.421
Total gastrectomy	1			
Postoperative complications (Score ≥Clavien-Dindo grade III)				
yes	2.651 (1.310□5.363)	0.007*	2.847 (1.129□7.480)	0.027*
no	1			
PTM stage				
□B	1.228 (0.284□5.317)	0.784	1.480 (0.307□7.141)	0.626
□A	2.233 (0.493□10.110)	0.297	2.082 (0.380□11.405)	0.398
□B	2.009 (0.474□8.521)	0.344	2.207 (0.428□11.384)	0.344
□C	1.919 (0.456□8.072)	0.374	1.258 (0.191□8.306)	0.811
□	5.115 (1.092□23.961)	0.038*	2.645 (0.379□18.477)	0.327
□B	1			
High Loss weight(kg)	0.946 (0.870□1.030)	0.200	/	/
Large Tumor size(cm)	1.118 (1.045□1.198)	0.001*	1.130 (1.032□1.239)	0.009*
High CA199(U/ml)	1.002 (1.000□1.003)	0.015*	1.001 (0.999□1.002)	0.336
High CA125(U/ml)	1.009 (1.002□1.016)	0.013*	1.005 (0.996□1.014)	0.260
Intraoperative blood transfusion				
yes	0.716 (0.397□1.291)	0.266	/	/
no	1			
High Lymphnode metastasis rate	2.497 (1.100□5.669)	0.029*	4.170 (0.669□25.987)	0.126
High NLR	1.185 (1.023□1.373)	0.024*	0.948 (0.734□1.225)	0.682
High PLR	1.002 (0.999□1.005)	0.161	1.002 (0.997□1.007)	0.385
High LMR	0.898 (0.825□0.977)	0.013*	0.923 (0.860□0.991)	0.027*
Long postoperative hospital stay	1.042 (0.992□1.095)	0.104	1.027 (0.967□1.091)	0.383

Footnotes: CI, confidence interval; NLR,neutrophil -to-lymphocyte ratio ;PLR,platelet -to lymphocyte ratio ;LMR,lympho-cyte -to- monocyte ratio ; CA19-9, carbohydrate antigen 19-9; CA 125, carbohydrate antigen 125, Clavien-Dindo grade, assesses the grade of postoperative complications□

*: $p < 0.05$.

Figures

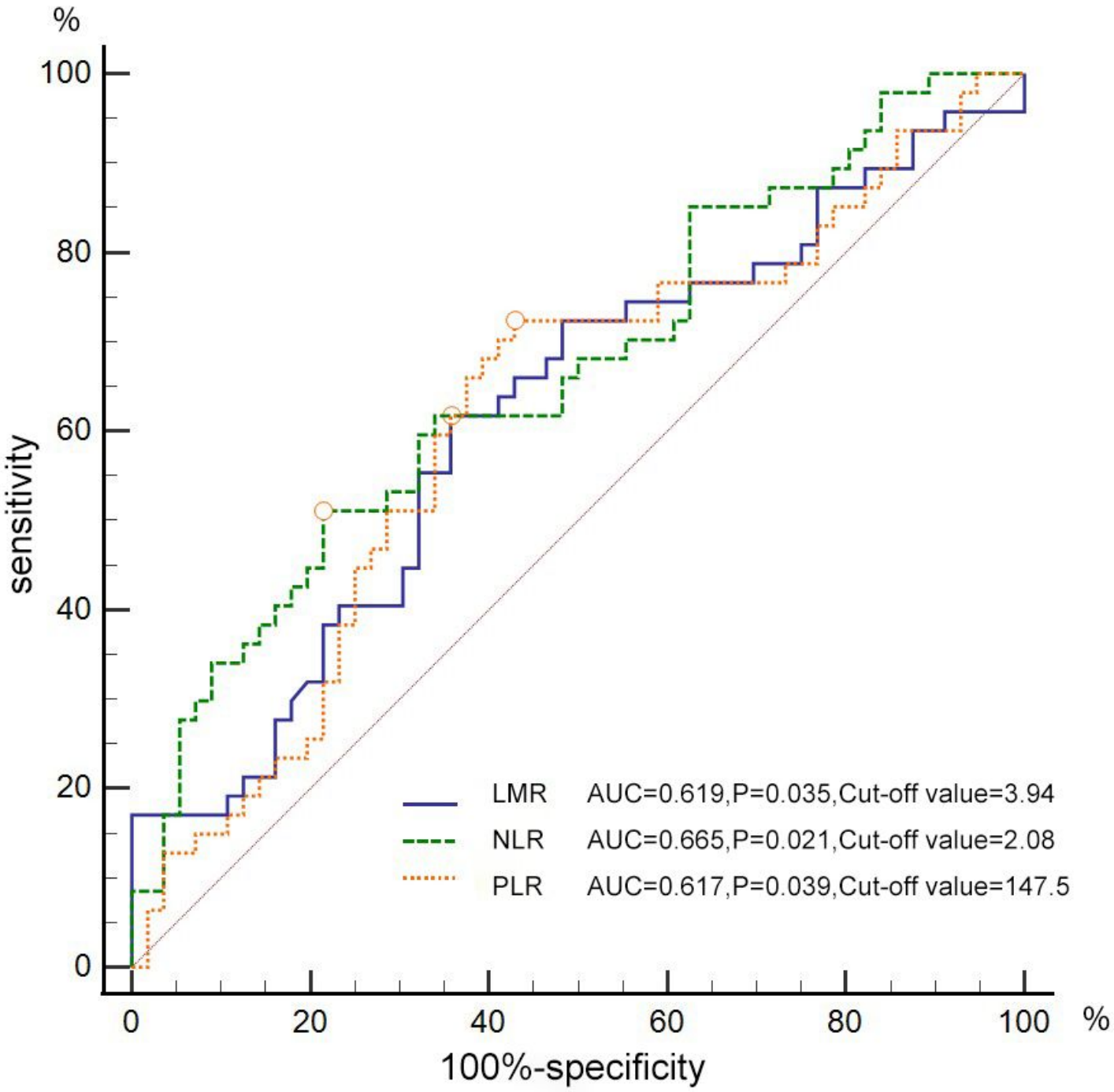

Figure 1

ROC curves for preoperative NLR,PLR, LMR. AUC: areas under the curve.

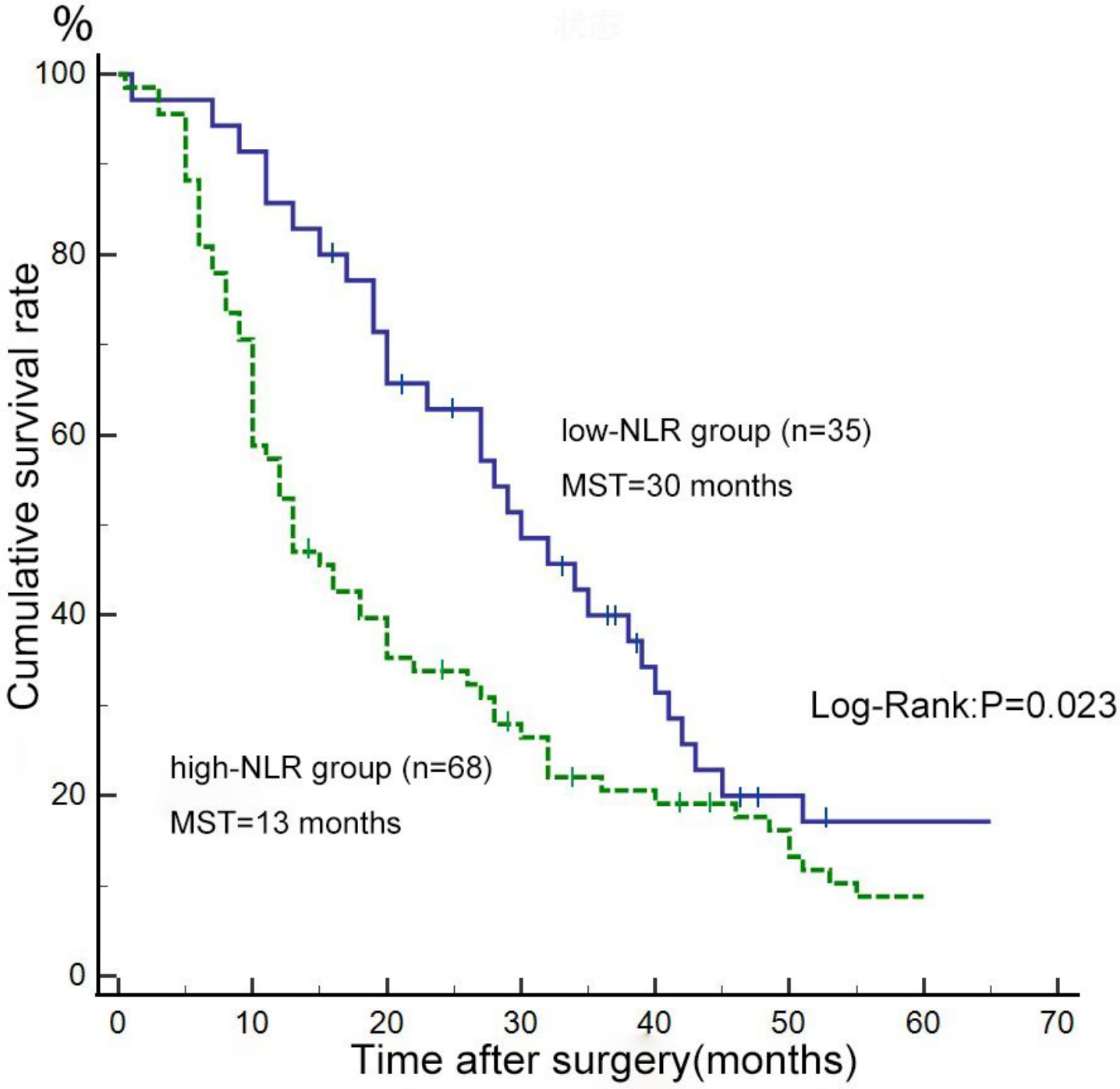

Figure 2

Kaplan-Meier survival curves for gastric neuroendocrine tumor patients. A significant difference was observed between the two groups when stratified by the preoperative NLR. MST, median survival time

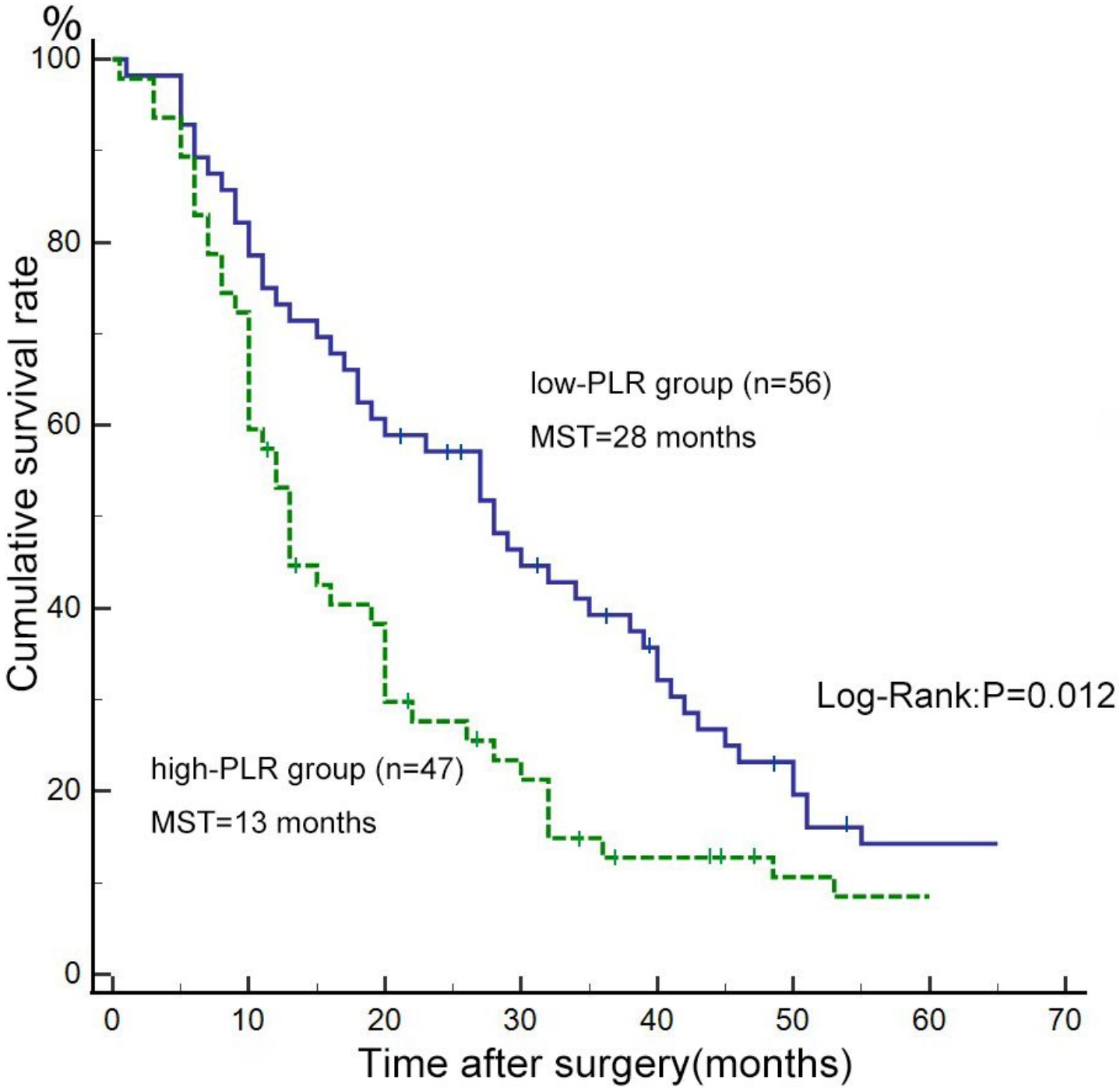

Figure 3

Kaplan-Meier survival curves for gastric neuroendocrine tumor patients. A significant difference was observed between the two groups when stratified by the preoperative PLR. MST, median survival time

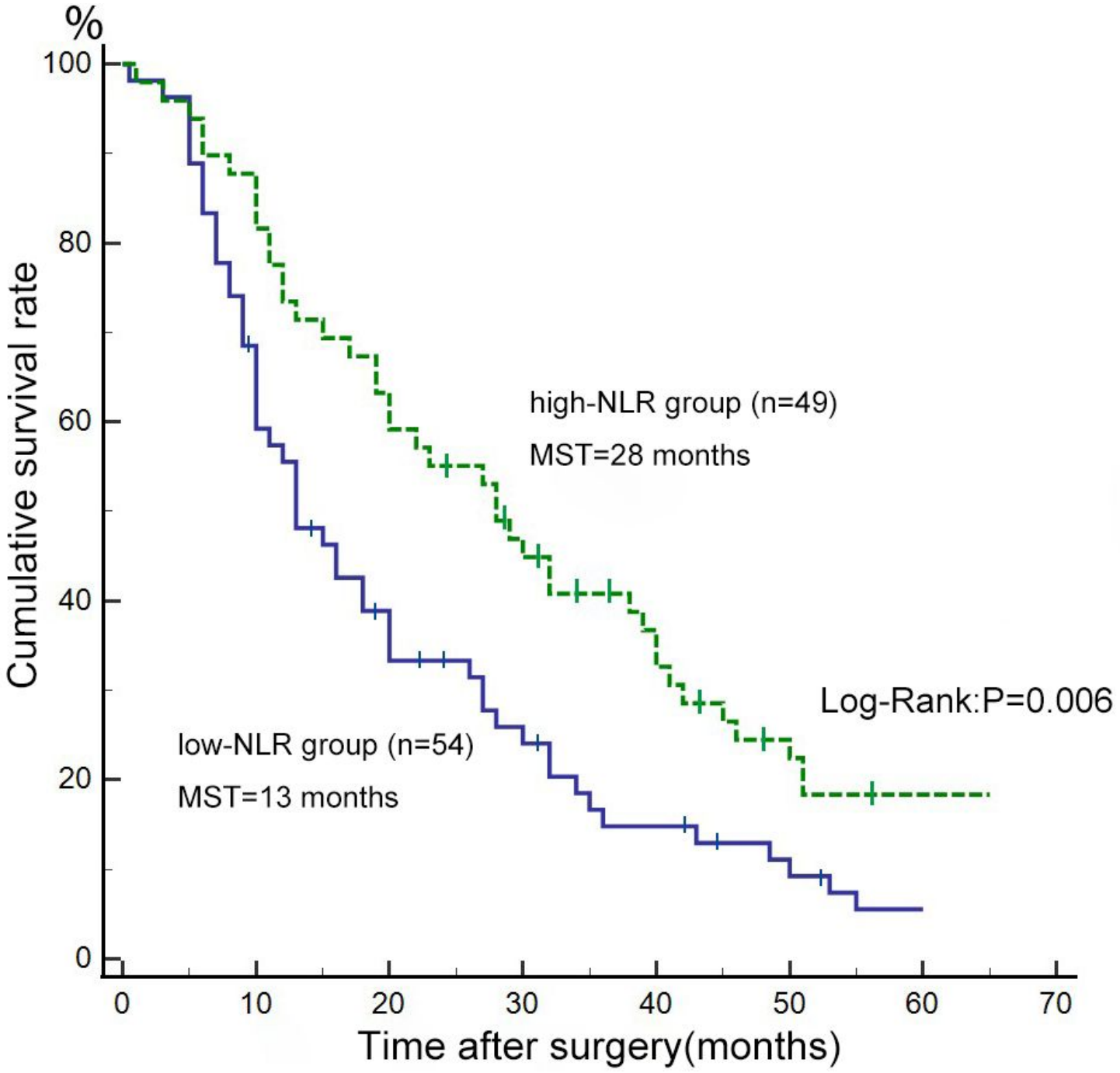

Figure 4

Kaplan-Meier survival curves for gastric neuroendocrine tumor patients. A significant difference was observed between the two groups when stratified by the preoperative LMR. MST, median survival time