The Preoperative Lymphocyte to Monocyte Ratio Predicts Clinical Outcome In Resected Patients With $T_{2-4}N_{0-3}M_0$ Siewert Type II/III Adenocarcinoma Of The Esophagogastric Junction

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Abstract

Background Inflammation has a critical role in the pathogenesis and progression of cancer. The lymphocyte to monocyte ratio (LMR) could be a new biomarker in various tumors.

Aims We analyzed the LMR with clinicopathological parameters and outcome in resected patients with $T_{2-4}N_{0-3}M_0$ Siewert type II/III of advanced adenocarcinoma of the esophagogastric junction (AEG) .

Methods A total of five hundred and seventy-one patients with Siewert type II/III of AEG between Jan 2006 and Jun 2012 were included in this retrospective study. Kaplan-Meier curves were used to calculate the cancer-specific survival (CSS). Univariate and multivariate Cox-regression analyses were performed to evaluate the prognostic factors.

Results We set 3.64 as the cut-off level based on the receiver operating characteristic curve. The preoperative absolute lymphocyte count tended to decrease in 'LMR≤3.64' group, and the preoperative absolute monocyte count tended to decrease in 'LMR3.64' group. The decreased preoperative LMR was significantly associated with decreased CSS in univariate (HR:2.311, 95%CI:1.639-3.254, *P*=0.008) and multivariate analysis (HR:1.642, 95%CI:1.242-2.171, *P*=0.027). According to the treatment regimen(surgery alone versus surgery and adjuvant chemotherapy), no significant difference in the 5-year CSS was identified in 'high-risk' group (LMR≤3.64) (HR: 1.121, 95%CI: 0.733-1.725, *P*=0.605).

Conclusions The LMR might be an independent prognostic marker for CSS in resected patients with $T_{2-4}N_{0-3}M_0$ Siewert type II/III of advanced AEG. When the 'high-risk' patients with LMR≤3.64 were analyzed, no benefit of adjuvant 5-FU-based chemotherapy could be found.

Introduction

In the recent decades the incidence of adenocarcinoma of the esophagogastric junction (AEG) has been increased in the worldwide[1]. Especially in China, due to the lack of routine screening, AEG is often diagnosed at the advanced staged(T2+) with or without lymph nodes metastasis and hematogenous dissemination[2], so the mortality caused by AEG is higher than the other gastrointestinal tumors. According to the distance between the tumor center and the anatomic esophagogastric junction(EGJ), AEG was divided into three subgroups by Siewert's classification[3]. Type I (adenocarcinoma of the distal esophagus with the tumor center located within 1 cm to 5 cm above the EGJ) is the most prevalent type in Western countries. It is often treated as distal esophageal cancer [4]. Type II (true adenocarcinoma of the cardiac with the tumor center located within 1 cm above and 2 cm below the EGJ) and the type III (subcardial adenocarcinoma that infiltrates the esophagogastric junction with the tumor center located within 2 cm and 5 cm below the EGJ) are more common than type and are mostly treated as proximal gastric cancer in China. Because of the different characteristics, the surgical technique and treatment strategies are different in three subgroups. Although the great development of radical surgery and adjuvant chemotherapy, long time survival rates for non-metastatic AEG range from 18 to 50 percent after

curative surgery [5]. In some trials, chemotherapy based on 5-fluorouracil with oxaliplatin or docetaxel may improve patient outcomes[6]. However, there are still a large number of advanced AEG patients after receiving radical surgery can not benefit from 5-fluorouracil-based chemotherapy[7]. The high mortality is primarily related to complications of tumor dissemination. As we all know, lots of studies evaluated the association of various biomarkers with clinical outcome in gastrointestinal tumor. Owing of high costs, lack of standardization, and limited availability, the biomarkers still can not come into routine clinical practice[8.9]. Some evidence revealed that tumor-associated inflammation could play an important role in cancer progression and prognosis. Previous studies have suggested that the preoperative peripheral blood cells can reflect the systemic inflammation, such as lymphocyte to monocyte ratio(LMR). Some studies show that survival benefit is associated with an increased pretreatment LMR [10, 11]. The LMR might be a good reflection of host's immune response and tumor burden. However, the prognostic value of the LMR in advanced AEG has not been reported. The aim of this study was to investigate the clinical significance and the prognostic value of the preoperative LMR for resected patients with $T_{2-4}N_{0-3}M_0$ Siewert type II/III of advanced AEG.

Materials And Methods

Patients and specimens

We conducted this study on consecutive patients with Siewert type and of AEG. A total of 708 patients with histologically confirmed AEG were included in this study. All patients were treated at the first ward of gastrointestinal surgery in The First Affiliated Hospital of Anhui Medical University from Jan 2006 to Jun 2012. In our hospital, type of AEG were treated at thoracic surgery as the distal esophageal cancer, type and were treated at gastrointestinal surgery. All the patients were in relatively fine overall conditions without severe dysfunction of important organs or systematic unfit like dyscrasia, rheumatic disease or hypohepatia. Patients undergoing multivisceral resection or having other gastroenteric diseases were excluded from our study. To avoid possible effects of such treatments on preoperative laboratory profiles those who had received neoadjuvant chemotherapy or received a blood product transfusion within one month before resection were also excluded. They also had not received any radiotherapy or interventional therapy before. Besides, patients were confirmed without severe mental disorders.

All enrolled patients underwent radical surgery. For type II adenocarcinomas invading the distal of esophagus, transhiatal total gastrectomy or proximal gastrectomy combined with mediastinal lymphadenectomy was preferred. Thoracoabdominal incision might be performed for subtotal esophagectomy to guarantee curability, if the frozen section of proximal esophageal cutting edge was positive. For type III AEG, transabdominal TG was performed in our department of gastrointestinal surgery. D2 lymphadenectomy was routinely performed. The inferior mediastinal or extended lymph node dissection was performed for patients with esophageal involvement. Intraoperative frozen section was a routine procedure aiming to secure the tumor cells free from the resection margins. All operations were

conducted by the same group of surgeons who routinely operated on more than 50 cases per year and who had surgical practice of 5 or more consecutive years.

After radical surgery, 453 patients received 4–6 cycles of frst-line adjuvant combination chemotherapy. 231 patients received 5-fluorouracil + leucovorin + oxaliplatin (FOLFOX), and 222 patients received a prodrug of 5-fluorouracil (capecitabine; CapeOX). The flow chart of study population was shown in Fig. 1.

Evaluation And Staging

Clinical stage was assessed according to computed tomography(CT) and ultrasound endoscope examinations. In our department, preoperational abdominal CT and ultrasound endoscope are examined routinely. After surgery, the tumor were staged according to the tumor-node-metastasis (TNM) criteria from the 7th edition of the International Union Against Cancer's classification.

Laboratory Date

As part of pretreatment evaluation, all patients' peripheral blood samples were collected into tubes containing dipotassium ethylenedinitrotetra-acetic acid (EDTA) at 3 days before surgery and all measurements were performed within 30 min after blood collection. The peripheral LMR was calculated as the ratio of absolute counts between peripheral lymphocytes and monocytes. Analysis of the white blood cell count was performed in the routine laboratory of our hospital (Sysmex XE-2100 Hematology Analyzer).

Follow-up

Enrolled patients were prospectively followed-up until Jun 2017. Follow-up was performed in regular intervals (every 3 months for the first 2 years after treatment, every 6 months intervals in 3–5 years and every 12 months intervals after 5 years). Follow-up evaluations included clinical check-up, laboratory including complete blood count (CBC), liver function test, and radiological assessment (liver scan and chest X-ray every 6 months). All of the clinical features were retrospectively obtained from the patients' history. Follow-up data were available.

Statistical analysis

As the current study described the prognosis of patients with AEG II/III, therefore, a cancer-specific survival (CSS) analysis was ascertained. The CSS was defined as the time from surgery to cancer-related death. The optimal cut off levels for the LMR were by applying receiver operating curve (ROC) analysis. The association between the clinic pathological features and the LMR with CSS was analyzed by using Kaplan-Meier curves and compared by the log-rank test. The clinic pathological features was correlated with the LMR by X^2-test. The multivariate analysis was performed using the Cox proportional hazards

regression. Hazard ratios (HRs) estimated from the Cox-regression analysis were reported as relative risks with corresponding 95% confidence intervals. All statistical analyses were performed using the Statistical Package for Social Sciences version 19.0(SPSS Inc, Chicago, IL, USA). A two-sides *P* value of < 0.05 was considered statistically significant.

Results

In our study, 708 patients were enrolled. 4 patients were excluded because they died of postoperative complications. 71 patients were belong to pT1 stage. 62 patients were lost to follow-up. At last, 571 patients were included in this study. 113(19.8%) were women and 458(80.2%) were men, with an age range from 28 to 89 years. The median age at time of diagnosis was 61.9 years. The median follow-up time was 63.5 months (range 1 to 115). The basic clinic pathological characteristics of patients are presented in Table 1.

Table 1
Association between clinicopathological parameters and LMR

Parameter	Overall	LMR>3.64	LMR ≤ 3.64	*P*-value
n	**571(%)**	**388(%)**	**183(%)**	
Gender				
Female	113(19.8)	87(22.4)	26(14.2)	0.021
Male	458(80.2)	301(77.6)	157(85.8)	
Age(years)				
≤ 65	357(62.5)	256(66.0)	98(53.6)	0.004
>65	217(37.5)	132(34.0)	85(46.4)	
Siwert type of AEG				
II	362(63.4)	244(62.9)	118(64.5)	0.712
III	209(36.6)	144(37.1)	65(35.5)	
Tumor length(cm)				
≤ 3	308(53.9)	225(57.9)	83(45.4)	0.005
>3	263(46.1)	163(42.1)	100(54.6)	
Vessel invasion				
Negative	461(80.7)	319(82.2)	142(77.6)	0.191
Positive	110(19.3)	69(17.8)	41(22.4)	
Nerve invasion				
Negative	504(88.3)	345(88.9)	159(86.9)	0.481
Positive	67(11.7)	43(11.1)	24(13.1)	
pT stage				
2	60(10.5)	41(10.6)	19(10.4)	0.008
3	108(18.9)	88(22.7)	20(10.9)	
4a	271(47.5)	172(44.3)	99(54.1)	
4b	132(23.1)	87(22.4)	45(24.6)	
pN stage				
0	158(27.7)	118(30.4)	40(21.9)	0.039
1	36(6.3)	21(5.4)	15(8.2)	

Parameter	Overall	LMR>3.64	LMR ≤ 3.64	*P*-value
2	149(26.1)	106(27.3)	43(23.5)	
3	228(39.9)	143(36.9)	85(46.4)	
pTNM satge				
IB	37(6.5)	25(6.4)	12(6.6)	0.022
IIA	55(9.6)	48(12.4)	7(3.8)	
IIB	61(10.7)	41(10.6)	20(10.9)	
IIIA	65(11.4)	48(12.4)	17(9.3)	
IIIB	123(21.6)	77(19.8)	46(25.1)	
IIIC	230(40.2)	149(38.4)	81(44.3)	
Adjuvant chemotherapy				
No	118(20.7)	61(15.7)	57(31.1)	< 0.001
Yes	453(79.3)	327(84.3)	126(68.9)	
Abbreviation: LMR = lymphocyte to monocyte ratio.				

Applying ROC curve analysis, the optimal cut-off levels for the LMR was 3.64 for CSS. The ROC curve was shown in Fig. 2. The area under the curve was 64.3% for CSS (P<0.001). Based on the optimum cut-off values of LMR, patients were divided into two groups for further analysis (Patients with a LMR ≤ 3.64 is the high-risk group and with a LMR>3.64 is the low-risk group). In our study cohort, clinic pathologic characters were compared between the 'high-risk' and 'low-risk' groups for LMR, we found significant associations between gender(P = 0.021), age(P = 0.004), tumor length(P = 0.005), pT stage(P = 0.008), pN stage(P = 0.039), pTNM stage(P = 0.022) and adjuvant chemotherapy(P < 0.001). (Table 1) The preoperative absolute neutrophil/lymphocyte/monocyte counts were shown in Table 2. The lymphocyte count tended to decrease in 'high -risk' group, and the monocyte count tended to decrease in 'low-risk' group. Of the 571 type II/III advanced AEG patients, 291(50.9%) died within the follow-up period, 104(56.8%) out of 183 patients with a LMR ≤ 3.64 and 187(48.2%) out of 388 patients with a LMR>3.64,respectively. As shown in Table 3, clinic pathological characters for prediction of CSS were further investigated by univariate analysis with Cox regression model. In univariate analysis, tumor length (P < 0.001), pT stage (P < 0.001;Figure 3A), pN stage (P < 0.001; Fig. 3B), vessel invasion (P = 0.027), pTNM stage (P < 0.001; Fig. 3C) and LMR (P = 0.008; Fig. 3D) were significantly associated with 5-year CSS (Table 3). Then all of the 6 variables above were included in a multivariate Cox proportional hazards model to adjust the effects of covariates. In that model, we demonstrated that pT stage (HR: 2.213, 95%CI: 1.315–3.724, P = 0.003), pTNM stage (HR: 2.449, 95%CI: 1.198–5.006, P = 0.014) and LMR (HR: 1.642, 95%CI: 1.242–2.171, P = 0.027) were independent prognostic factors in patients with advanced type II/III AEG (Table 3). To evaluate if Siewert type II/III advanced AEG patients benefit from adjuvant chemotherapy after radical surgery compared with surgery alone, Kaplan-Meier analysis and log-rank test

were performed. The 5-year CSS of all patients in 'high-risk' group (LMR ≤ 3.64) was 43.2% compared with 51.8% in 'low-risk' group (LMR>3.64) (HR: 2.311, 95%CI: 1.639–3.254, *P* = 0.008; Fig. 3D). In our cohort, 453(79.3%) out of 571 patients received the adjuvant chemotherapy after radical surgery. In 'low-risk' group (LMR>3.64), the 5-year CSS in patients with surgery and adjuvant chemotherapy was 58.2% compared with 37.2% in patients with surgery alone (HR: 0.435, 95%CI: 0.223–0.732, *P* < 0.001; Fig. 4A). According to the treatment regimen(surgery alone versus surgery and adjuvant chemotherapy), no significant difference in the 5-year CSS was identified in 'high-risk' group (LMR ≤ 3.64) (HR: 1.121, 95%CI: 0.733–1.725, *P* = 0.605; Fig. 4B).

Table 2
The preoperative absolute neutrophil/lymphocyte/monocyte counts

Parameter	Overall	LMR>3.64	LMR ≤ 3.64
Total leucocyte count($X10^9$/L)	5.9 ± 1.9;5.6(1.3–18.3)	5.6 ± 1.7;5.5(1.3–18.3)	6.1 ± 2.2;5.6(2.7–12.1)
Neutrophil count($X10^9$/L)	3.8 ± 1.8;3.4(0.9–15.3)	3.4 ± 1.3;3.3(0.9–10.3)	4.2 ± 2.0;3.9(1.3–15.3)
Lymphocyte count ($X10^9$/L)	1.7 ± 0.5;1.5(0.5–4.1)	1.9 ± 0.5;1.9(1.3–4.1)	1.4 ± 0.4;1.3(0.5–3.7)
Monocyte count ($X10^9$/L)	0.4 ± 0.1;0.3(0.1–1.1)	0.3 ± 0.1;0.3(0.1–0.9)	0.4 ± 0.1;0.4(0.2–1.1)
Platelet count($X10^9$/L)	189 ± 78;187(55–560)	190 ± 74;186(60–463)	191 ± 81;188(55–560)
Hemoglobin(g/L)	122 ± 22;126(70–156)	124 ± 23;122(75–156)	118 ± 20;118(70–146)
Abbreviation: LMR = lymphocyte to monocyte ratio.			

Table 3
Univariate and multivariate analysis of LMR for CSS in patients with type II/III of advanced AEG

	Univariate analysis		Multivariate analysis	
Parameter	**HR(95%CI)**	P-**value**	**HR(95%CI)**	P-**value**
Gender				
Female	1(reference)	0.592		
Male	1.082(0.811–1.443)			
Age(years)				
≤ 65	1(reference)	0.227		
>65	1.150(0.917–1.443)			
Siewert type of AEG				
II	1(reference)	0.288		
III	0.882(0.699–1.112)			
Tumor length(cm)				
≤ 3	1(reference)	< 0.001	1(reference)	0.696
>3	3.753(2.299–6.127)		1.059(0.793–1.415)	
pT stage				
T2	1(reference)	< 0.001	1(reference)	0.003
T3	2.131(1.550–4.784)		2.213(1.315–3.724)	
T4a	4.179(2.102–8.307)		T2 versus T3-4	
T4b	6.121(3.134–11.956)			
pN stage				
N0	1(reference)	< 0.001	1(reference)	0.214
N1	1.109(0.586–2.099)		0.862(0.683–1.089)	
N2	1.641(1.176–2.289)		N0 versus N1-3	
N3	3.031(2.282–4.027)			
pTNM stage				
I	1(reference)	< 0.001	1(reference)	0.014
II	2.987(1.698–5.254)		2.449(1.198–5.006)	

	Univariate analysis		Multivariate analysis	
III	5.148(3.100-8.549)		I versus II + III stage	
Vessel invasion				
negative	1(reference)	< 0.001	1(reference)	0.180
positive	1.872(1.371–2.557)		0.852(0.674–1.077)	
Nerve invasion				
negative	1(reference)	0.319		
positive	1.156(0.869–1.538)			
LMR				
>3.64	1(reference)	0.008	1(reference)	0.027
≤ 3.64	2.311(1.639–3.254)		1.642(1.242–2.171)	
Adjuvant chemotherapy				
Yes	1(reference)	0.351		
No	1.151(0.857–1.541)			
Abbreviations:CCS = cancer-specific survival; LMR = lymphocyte to monocyte ratio;				

Discussion

Recently, systemic inflammation has been found to correlate with tumor progression. Leucocytes in the tumor microenvironment promote tumor growth, angiogenesis and metastasis[12] Many peripheral inflammatory markers including PLR, NLR and LMR and their prediction of clinical outcomes in solid tumor entities have been uncovered [13, 14] In this study, we examined a large cohort of patients with advanced type/ AEG and investigated the prognostic significance of preoperative lymphocyte to monocyte ratio as a biomarker for predicting the outcomes after radical surgery.

As we all know, lymphocytes play an essential role in systemic inflammatory response to tumorous disease, including the inhibition of tumor cell proliferation and migration [15]. lymphocytes are the important components of the adaptive and innate immune system and the cellular basis of immunosurveillance. A decreased lymphocyte count is assumed to reflect an insufficient immunologic reaction to the tumor, thus promoting tumor cell apoptosis and metastasis [16].Some studies have shown a prognostic impact of tumor-infltrating lymphocytes (TILs) in a series of cancers including gastric

cancer[17, 18]. In the study of gastric adenocarcinoma, dense infltration of CD3 + and CD8 + TILs had been associated with an optimistic prognosis [17]. In esophageal adenocarcinoma, the lower level of the FOXP3 + regulatory T cell (Treg) infltrate present in the residual tumor or scar correlated with the more pathological response [19]. In resent study, Higher levels of TILs in the pathological specimen were associated with signifcant pathological response to neoadjuvant chemotherapy (NAC), increased levels of CD4 + and CD8 + TILs were associated with signifcant local tumour regression and lymph node downstaging[20].

The role of monocytes in tumor invasion, proliferation and metastasis is important. Monocytes can differentiate into tumor-associated macrophages(TAMs) in the tumor microenvironment. TAMs are recruited at the tumor site, where they accelerate tumor progression through the angiogenesis and anti-immune responses[21]. More and more evidence show that tumor-associated macrophages(TAMs) suppress the immune system of the host and promote tumor angiogenesis, proliferation and migration [22]. Macrophages are capable of producing osteonectin, which is essential in forming metastasis. This evidence suggests a tumorous potential of monocytes due to formation of different macrophage phenotypes that promote the malignant process. The high absolute monocytes count in the peripheral blood is reported to stand for the formation of TAMs and an elevated tumor burden in patients[23]. Therefore, it is not surprising that peripheral blood monocytosis is an adverse prognostic factor for various tumors. The LMR might be a good reflection of responsiveness of the immune system of the host and a microenvironment marker of tumor burden. The prognostic values of LMR in patients with AEG remain uncertain.

In our study, we set 3.64 as the cut-off levels for the LMR by applying ROC curve analysis, different from some other studies, such as 4.0 in the study by Hirahara N[24], 2.86 in pancreatic adenocarcinoma by Li's study[25], a decreased peripheral lymphocyte to monocyte ratio (LMR) has been identifed as a poorer prognostic indicator in various cancers[26, 27].From Table 2, we found that the median of Lymphocyte count was higher in 'LMR≥3.64'(1.9) than in 'LMR ≤ 3.64'(1.3). The median of monocyte count was nearly the same in two groups(0.3vs0.4). 5-year CSS with 'LMR≥3.64' was 51.8% higher than 43.2% with 'LMR ≤ 3.64' (P = 0.008; Fig. 2D). Sometimes TAMs not only enhance tumor growth and progression, but also modulate the efficacy of various forms of anticancer therapy, such as chemotherapy and radiotherapy. In some circumstances, they also facilitate tumor regrowth, revascularization, and spread after the treatment[28]. In patients with esophageal cancer, infiltration with CD68 + and CD163 + TAMs, especially M2 macrophages, is associated with a poor prognosis for patients undergoing neoadjuvant chemotherapy[29]. Not only the first-line chemotherapeuitc drug, but also epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) had a poor response in patients with advanced non-small cell lung cancer[30]. As we all know, how to predict whether patients of AEG can benefit from chemotherapy was still a problem which perplexed physicians for many years. Our results suggest that 'high-risk' patients based on LMR ≤ 3.64 do not benefit from 5-fluorouracil-based adjuvant chemotherapy. For high-risk patients of AEG, we should avoid to use of adjuvant 5- fluorouracil -based chemotherapy

until disease progression. Moreover, the LMR provides an easy available and low price biomarker with outcome.

To the best of our knowledge this is the first study to assess the LMR in advanced type II/III AEG. The strength of this study is the large sample size and the long follow-up period. However, there are some possible limitations associated with this study. Firstly, because of the retrospective design of the study, we cannot fully exclude the selection bias in our cohort. Furthermore, potential confounding factors such as infection, coronary syndrome, and diabete mellitus, that might affect the lymphocyte and monocyte count were not taken into consideration. Finally, although we set 3.64 as the cut-off level by using ROC curve, different cut-off levels may also valuable. So large prospective and multi-centric clinical trails should be performed to confirm our findings in future.

Declarations

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Author's contributions

Jiawei Zhang contributed to study concept and design, data acquisition, analysis and interpretation, statistical analysis, and manuscript writing; Ke Chen,Bo Chen, Maoming Xiong and Aman Xu involved in data acquisition and manuscript critical revision. All the authors reviewed and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interests.

Ethics standards

This research was permitted by the Ethical Committee of the First Affiliated Hospital of An Hui Medical University. Written informed consent was obtained from each patient. The study complied with current Chinese law and was performed in accordance with the principles of Declaration of Helsinki(1964).

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Figures

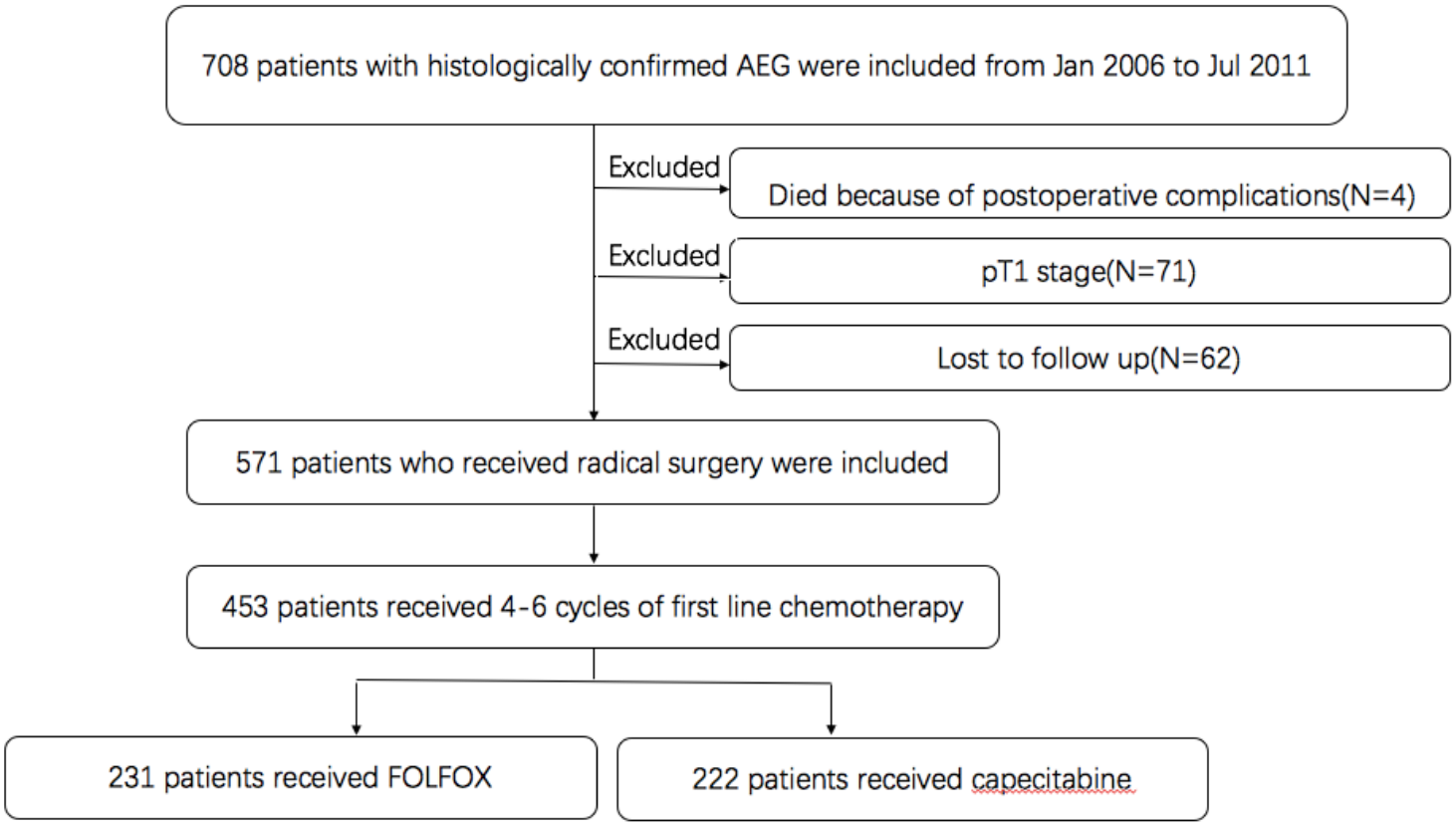

Figure 1

Flow chart of study population

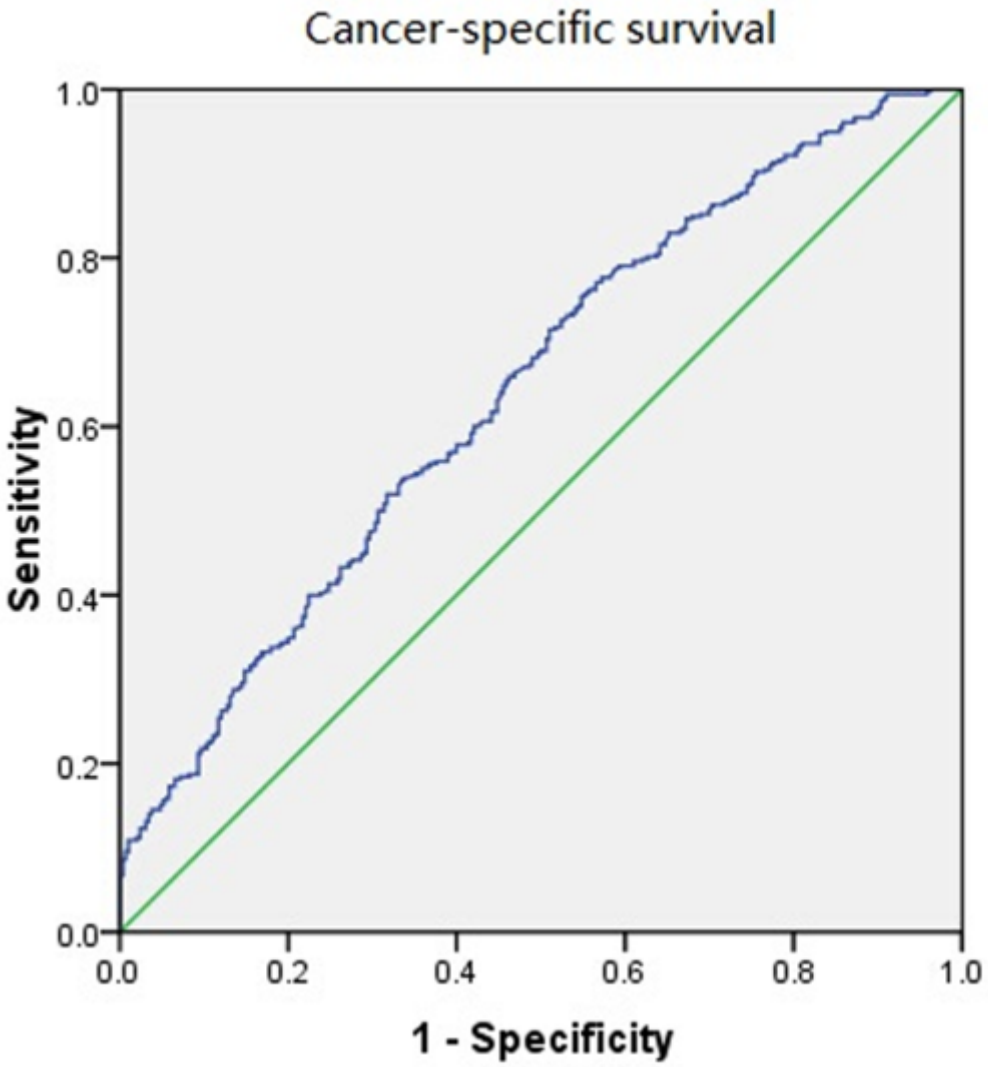

Figure 2

Receiver-operator characteristic curve for CSS were plotted to verify the optimum cut-off values for LMR

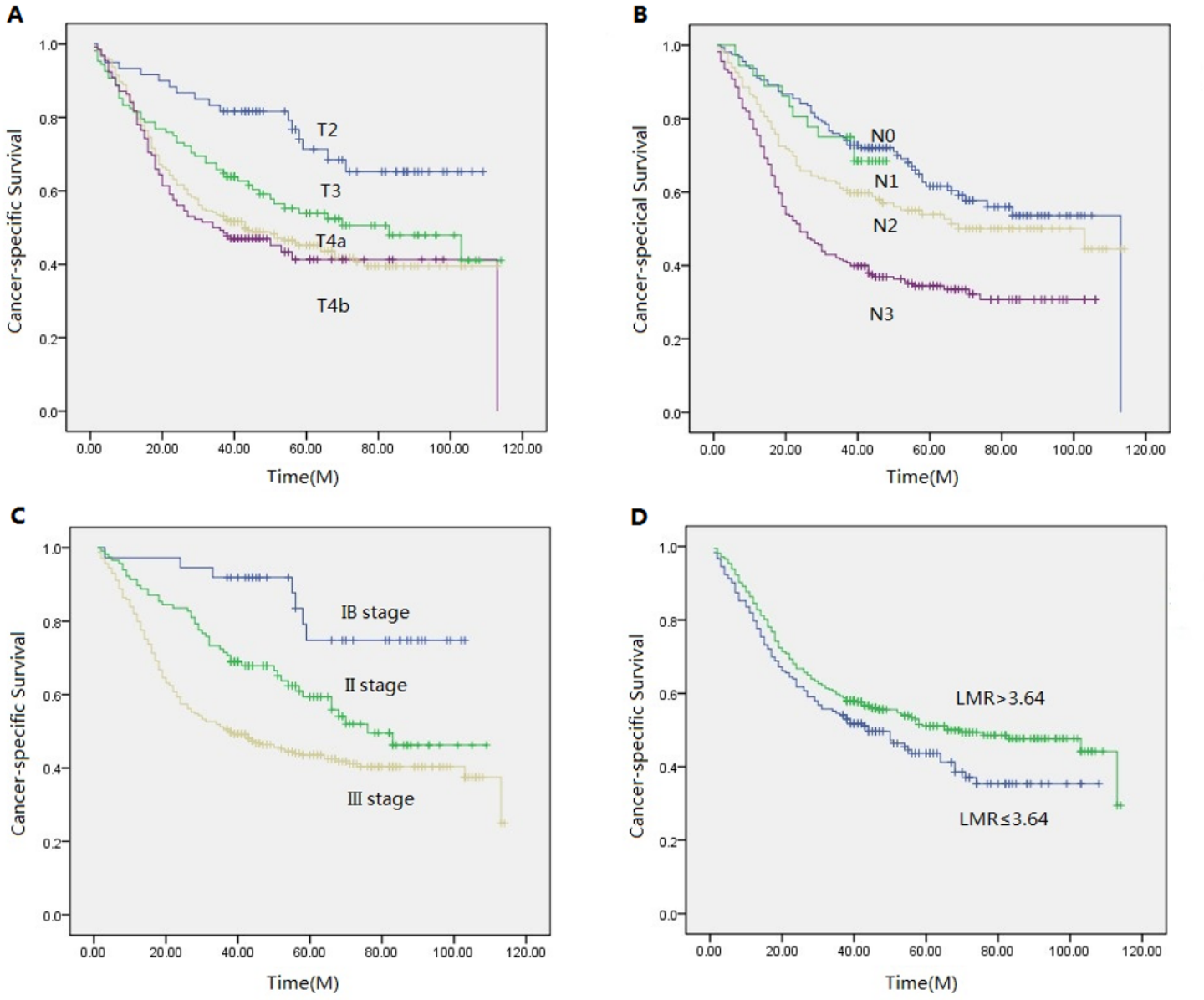

Figure 3

Kaplan-Meier analysis of cancer-specific survival (CSS) curves stratified by pT stage(A), pN stage(B), pTNM stage(C), LMR(D). The 5-year CSS in patients with pT2, 3,4a and 4b were 71.3%, 52.4%, 44.0% and 39.6%, respectively (P<0.001). The 5-year CSS in patients with pN0, 1, 2 and 3 were 61.6%, —%, 53.9% and 34.4%, respectively (P<0.001). The 5-year CSS in patients with pIB stage, II stage and III stage were 74.7%, 59.4% and 43.6%, respectively (P<0.001). The 5-year CSS in patients with LMR>3.64 and LMR≤3.64 were 51.1% and 43.7%, respectively (P=0.008).

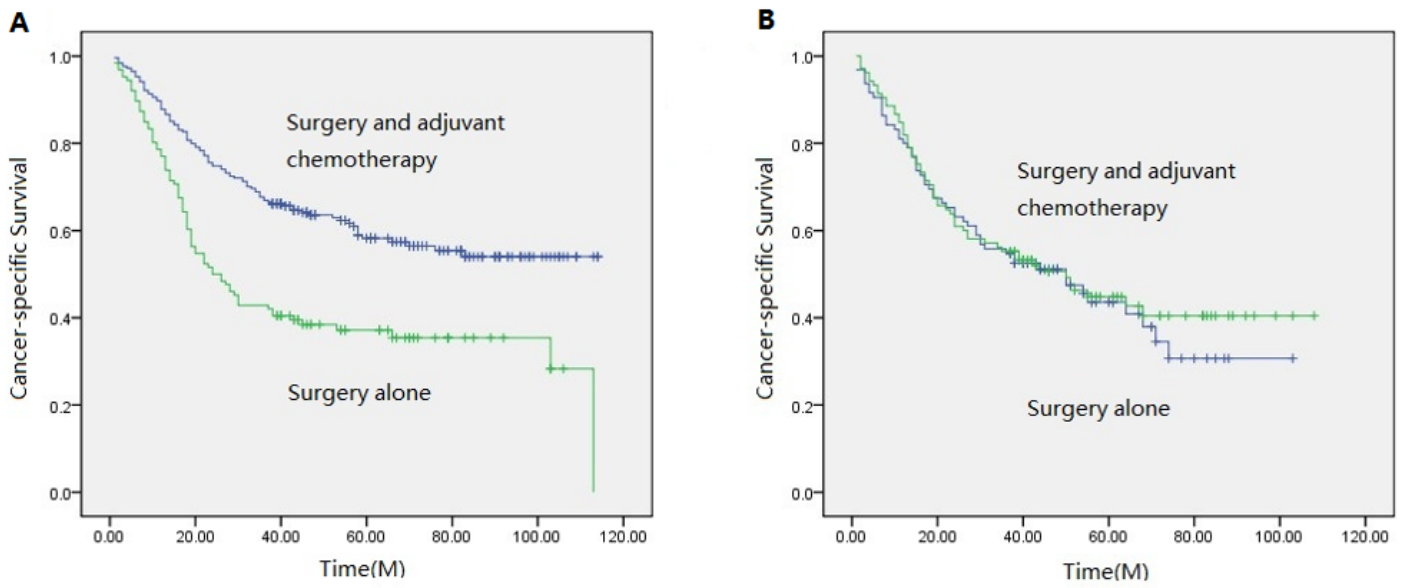

Figure 4

Association between adjuvant chemotherapy or surgery alone and cancer-specific survival (CSS) in 'low-risk' patients based on LMR>3.64(A) , (HR: 0.435, 95%CI: 0.223-0.732, P<0.001); in 'high-risk' patients based on LMR≤3.64(B) , (HR: 1.121, 95%CI: 0.733-1.725, P=0.605).