Prognostic value and association of systemic inflammation for patients with stage IV gastric cancer

C. Huang[1*], Z. Li[2*], Z. Zhang[1], X. Xia[1], D. Xu[1], A. Zhao[2], G. Zhao[1]

(1) Department of Gastrointestinal Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China ; (2) Department of Oncology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China.

Abstract

Objective **: The present study is aimed at investigating the prognostic value and association of systemic inflammation (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and lymphocyte-to-monocytes ratio) for patients with stage IV gastric cancer.**

Methods **: In this retrospective study, patients with stage IV gastric cancer between January 2008 and December 2017 were included. A summary was performed on clinicopathological characteristics and a multivariate cox regression analysis was performed to identify the prognostic factors.**

Results **: 304 patients with stage IV gastric cancer were included in the study. On multivariate analysis, the systemic chemotherapy ($p < .001$), the jaundice ($p = .004$), the high neutrophil-to-lymphocyte ratio ($p = .005$) and the high platelet-to-lymphocyte ratio ($p = .041$) were independent prognostic factors for patients with stage IV gastric cancer.**

Conclusion **: As systemic inflammation response markers, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are significantly associated with OS for stage IV gastric cancer patients. Systemic chemotherapy shows a clear overall survival benefit in patients with stage IV gastric cancer and Jaundice indicates poor overall survival.** (Acta gastroenterol. belg., **2020**, 83, **255-263**).

Keywords : stage IV gastric cancer, systemic inflammatory response, systemic inflammatory.

Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third most common cause of cancer-related death worldwide (1). The survival of patients with advanced GC is poor, whereas the prognosis of stage IV GC is worse (2). The latest studies have displayed that the presence of tumor-infiltrating immune and inflammation cells affected the survival of patients with solid malignancies (3,4).

The theory that GC represents an inflammation-driven malignancy has been proven (5-7), indicating the systemic inflammatory response (SIR) might be applied to the diagnosis and prognosis of GC. The involvement of the neutrophils, platelets, monocytes and lymphocytes may represent the neoplastic progression. Neutrophilia, thrombocytosis, monocytosis and lymphocytopenia all mark the progression of the malignancies to the advanced stage. Hence, the combination of lymphocytes, neutrophils, platelets and monocytes has been investigated to be an independent prognostic factor in determining the progression of malignancies (8,9). Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are separately calculated as neutrophil or platelet counts divided by lymphocyte counts. Lymphocyte-to-monocytes ratio (LMR) is calculated as lymphocyte counts divided by monocyte counts.

In this study, we retrospectively investigated the prognostic value and association of systemic inflammation (NLR, PLR and LMR) for patients with stage IV GC.

Patients and methods

Population

We retrospectively reviewed data collected from patients who were diagnosed as stage IV GC at Renji Hospital Shanghai Jiao Tong University School of Medicine from January 2008 to December 2017. The study was approved by Shanghai Jiaotong University of medicine, Renji Hospital Ethics Committee (No. 2017-114).

The following inclusion criteria were applied : (a) adenocarcinoma of the stomach was histologically confirmed ; (b) evidence of tumors invading adjacent organs, paraaortic lymph node enlargement or distant metastasis prove by abdominal computed tomography and/or abdominal ultrasound and posteroanterior chest radiography. (c) no prior chemotherapy, radiotherapy, or related surgical procedure ; (d) Eastern Cooperative Oncology Group performance status 0-1 ; (e) provision of signed written informed consent. Exclusion criteria were as follows : patients with incomplete or inaccurate medical records. Totally, 304 patients were included in the study. Staging of GC was performed under the corresponding eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual.

Correspondence to : Gang Zhao, Department of Gastrointestinal Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine, No.160 Pujian Road, Pudong New Area, Shanghai 200127, China.
E-mail : Zhaogang74313@126.com
Aiguang Zhao, Department of Oncology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, No. 725 Wanping South Road, Xuhui District, Shanghai 200032, China.
E-mail : aiguangzhao@qq.com
*Equal contributors

Submission date : 28/08/2019
Acceptance date : 24/01/2020

Markers of Systemic Inflammation

All the laboratory parameters were obtained before treatment, such as neutrophil count, lymphocyte count, platelet count. This research took 3 SIR markers into consideration. The NLR was defined by dividing the neutrophil count by the lymphocyte count. The PLR was defined by dividing the platelet count by the lymphocyte count. The LMR was defined by dividing the lymphocyte count by the monocyte count. The optimal cutoff values for the three SIR markers were calculated by the X-tile software (10), and were 2.1, 107.7, and 5.2, separately.

Follow-up Investigation

The follow-up assessment was performed every 3 months, for 2 years, and then every 6 months, for the following 3 years. In December 2017, the final follow-up evaluation was conducted. Follow-up appointments usually contained a physical examination, laboratory testing (including blood routine test, liver and kidney function, cancer antigen CA19-9, CA125, and carcinoembryonic antigen level measurements), abdominopelvic ultrasonography or computed tomography, and chest radiography, including an annual endoscopic examination. Overall survival (OS) was defined as the time from definitude diagnosis to death from any cause or to the time of censoring on the date of the last follow-up.

Immunohistochemistry

The histological diagnosis was performed on formalin-fixed and paraffin-embedded gastric cancer tissue blocks from pretreatment biopsies and gastrectomy. All Immunohistochemistry analyses were carried out at the Department of Pathology, Renji Hospital, Shanghai Jiaotong University. All IHC analyses were evaluated by light microscopy blindly and independently by 2 pathologists. The antibodies were : mouse monoclonal antibody against P53 (clone DO-7 ; Maxim, Fujian, China) ; mouse monoclonal antibody against Ki-67 (clone MIB-1 ; Aoqvan, Guangdong, China) ; rabbit monoclonal antibody against HER-2/NEU (clone 4B5 ; Roche , Tucson, USA) ; rabbit monoclonal antibody against EGFR (clone 5B7 ; Roche, Tucson, USA). The staining was scored as the intensity of the positive staining ("-" - negative, "+" - weak, "++" - moderate, "+++" - strong) multiplied by the staining areas. P53 ("-" <5% ; "+" >=5%, <25% ; "++" >=25%, <50%, "+++" >=50%) ; Ki-67 ("-" <5% ; "+" >=5%, <25% ; "++" >=25%, <50%, "+++" >=50%) ; HER-2 assessments were conducted according to the China Society of Clinical Oncology (CSCO) clinical guideline ; EGFR ("-" <10% ; "+" >=10%).

Statistical analysis

Descriptive statistics were used to summarize markers of systemic inflammation and other cohort characteristics. The optimal cutoff levels for NLR, PLR and LMR were calculated by the X-tile software (Yale University, New Haven, CT)[10). Categorical variables were analyzed using the chi-square or Fisher's exact test, whereas continuous variables were analyzed using Student's t-tests. Survival curves were constructed according to the Kaplan-Meier method, and differences between curves were analyzed using the log-rank test. Variables that significantly affected survival were investigated using multivariate analysis, according to the Cox regression model. All tests were two-sided, and statistical significance was inferred at a p-value of $< .05$. Statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL) and R ver. 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinicopathological Characteristics

Of the 304 patients with stage IV GC included in the study, 198 (65.1%) were men and 106 (34.9%) were women ; their median age was 60 years (interquartile range, 51-67). The tumor is most commonly located in the middle of the stomach, followed by the lower part of the stomach and then the upper part of the stomach. The Differentiation was as follows : 22 (7.2%) patients with Medium differentiation G2, 124 (40.8%) with poorly differentiated G3, and 3 (1.0%) with Undifferentiated G4. The peritoneal is the most common site of metastasis. 248 (81.6%) patients did systemic chemotherapy after diagnosis. About one-third of patients suffer from anemia. Most patients have no hypoproteinemia and jaundice (Table 1).

The correlation between markers of systemic inflammation and clinicopathological features

An increased NLR (NLR $\geq$ 2.1) was associated with male patients ($p = 0.011$, Table 3). An increased PLR (PLR $\geq$ 107.7) was associated with Her2 ($p = 0.002$, Table 4), while an increased LMR (LMR $\geq$ 5.2) was associated with female patients ($p < 0.001$, Table 5).

Survival Analysis

The median follow-up period was 28.01 months (range, 1-99). The 3-year OS rate for the entire cohort was 13.5%. The 2-year OS rate for the entire cohort was 21.0%. The 1-year OS rate for the entire cohort was 44.2%. Univariate analysis showed that Systemic chemotherapy, NLR and PLR were associated with OS (all $p < .05$, Table 2). In multivariate analyses, the systemic chemotherapy (hazard ratio (HR), 0.337 ; 95% confidence interval (CI), 0.245-0.464 ; $p < .001$) , the jaundice (hazard ratio (HR), 1.593 ; 95% confidence interval (CI), 1.159-2.189 ; $p = .004$), the high NLR (NLR $\geq$ 2.1 ; hazard ratio (HR),

Table 1. — **Clinicopathological features of the patients**

Clinicopathological features		**All patients (n=304)**	**(%)**
Age(years)	Median age	60 (interquartile range, 51-67)	20-88(range)
	<65	204	67.1
	>=65	100	32.9
Gender	Male	198	65.1
	Female	106	34.9
Tumor location	Upper	51	16.8
	Middle	133	43.8
	Lower	106	34.9
	Leather stomach	11	3.6
	Na	3	1.0
Differentiation	Medium differentiation G2	22	7.2
	Poorly differentiated G3	124	40.8
	Undifferentiated G4	3	1.0
	Na	155	51.0
Metastatic sites	Peritoneal	155	51.0
	Distant Lymph Node	53	17.4
	Liver	78	25.7
	Lung	6	2.0
	Bone	7	2.3
	Ovarian	16	5.3
	Pancreas	13	4.3
	Others	33	10.8
Systemic chemotherapy	No	56	18.4
	Yes	248	81.6
Anemia	Hb>=110(g/L)	192	63.2
	Hb<110(g/L)	112	36.8
Jaundice	TBil:1.7-17.1(μmol/L)	260	85.5
	TBil:17.1-34.2(μmol/L)	33	10.9
	TBil >34.2(μmol/L)	6	2.0
	Na	5	1.6
Hypoproteinemia	Alb>=35.0(g/L)	242	79.6
	Alb<35.0(g/L)	58	19.1
	Na	4	1.3
NLR	<2.1	77	25.3
	>=2.1	227	74.7
PLR	<107.7	41	13.5
	>=107.7	263	86.5
LMR	<5.2	270	88.8
	>=5.2	31	10.2
	Na	3	1.0
P53	-	52	17.1
	+	35	11.5
	++	19	6.3
	+++	54	17.8
	Na	144	47.4
KI67	-	8	2.6
	+	29	9.5
	++	54	17.8
	+++	102	33.6
	Na	111	36.5
Her2	-	102	33.6
	+/-	4	1.3
	+	36	11.8
	++	13	4.3
	+++	15	4.9
	Na	134	44.1
EGFR	-	28	9.2
	+/-	3	1.0
	+	44	14.5
	++	1	.3
	Na	228	75.0

Table 2 — **Univariate and multivariate analysis of clinicopathologic variables in relation to overall survival in patients of stage IV gastric cancer**

Clinicopathological features	Univariate analysis		Multivariate analysis	
	HR (95%)	*P* value	HR (95%)	*P* value
Age(years)				
<65				
>=65	1.236(0.942-1.622)	0.126		
Gender				
Male				
Female	0.944(0.758-1.304)	0.966		
Primary site of tumor				
Upper				
Middle				
Lower				
Leather stomach	0.935(0.786-1.112)	0.449		
Differentiation				
Medium diff G2				
Poorly diff G3				
Undiff G4	1.035(0.621-1.725)	0.894		
Peritoneal metastasis				
No				
Yes	1.018(0.785-1.321)	0.891		
Liver metastasis				
No				
Yes	0.957(0.823-1.112)	0.564		
Number of metastatic sites				
1				
>=2	1.034(0.771-1.387)	0.821		
Number of metastatic sites				
1,2				
>=3	1.245(0.886-1.750)	0.207		
Systemic chemotherapy				
No				
Yes	0.401(0.294-0.547)	<0.001	0.337(0.245-0.464)	<0.001
Anemia				
Hb>=110(g/L)				
Hb<110(g/L)	1.129(0.864-1.474)	0.375		
Jaundice				
TBil:1.7-17.1(μmol/L)				
TBil:17.1-34.2(μmol/L)				
TBil >34.2(μmol/L)	1.367(0.995-1.877)	0.053	1.593(1.159-2.189)	0.004
Hypoproteinemia				
Alb>=35.0(g/L)				
Alb<35.0(g/L)	1.225(0.891-1.685)	0.211		
NLR				
<2.1				
>=2.1	1.494(1.101-2.029)	0.010	1.579(1.150-2.168)	0.005
PLR				
<107.7				
>=107.7	1.648(1.079-2.518)	0.021	1.590(1.019-2.481)	0.041
LMR				
<5.2				
>=5.2	0.696(0.444-1.092)	0.115		
P53				
-				
+				
++				
+++	0.935(0.807-1.083)	0.368		
KI67				
-				
+				
++				
+++	0.947(0.793-1.132)	0.552		
Her2				
-				
+/-				
+				
++				
+++	0.914(0.766-1.092)	0.322		
EGFR				
-				
+/-				
+				
++	1.01(0.75-1.358)	0.949		

Table 3. — **The correlation between NLR and clinicopathological features**

	NLR		
Clinicopathological features	**<2.1**	**>=2.1**	**P value**
Age,n(%)			0.303
<65	48(62.3)	156(68.7)	
>=65	29(37.7)	71(31.3)	
Gender,n(%)			0.011
Male	41(53.2)	157(69.2)	
Female	36(46.8)	70(30.8)	
Primary site of tumor,n(%)			0.167
Upper	17(22.1)	34(15.2)	
Middle	38(49.4)	95(42.4)	
Lower	20(26.0)	86(38.4)	
Leather stomach	2(2.6)	9(4.0)	
Differentiation,n(%)			0.976
Medium diff G2	6(14.3)	16(15.0)	
Poorly diff G3	35(83.3)	89(83.2)	
Undiff G4	1(2.4)	2(1.9)	
Systemic chemotherapy,n(%)			0.865
No	15(19.5)	41(18.1)	
Yes	62(80.5)	186(81.9)	
Anemia,n(%)			0.357
Hb>=110(g/L)	52(67.5)	140(61.7)	
Hb<110(g/L)	25(32.5)	87(38.3)	
Jaundice,n(%)			0.711
TBil:1.7-17.1(μmol/L)	65(85.5)	195(87.4)	
TBil:17.1-34.2(μmol/L)	10(13.2)	23(10.3)	
TBil >34.2(μmol/L)	1(1.3)	5(2.2)	
Hypoproteinemia,n(%)			0.056
Alb>=35.0(g/L)	67(88.2)	175(78.1)	
Alb<35.0(g/L)	9(11.8)	49(21.9)	
P53,n(%)			0.344
-	11(28.2)	41(33.9)	
+	6(15.4)	29(24.0)	
++	5(12.8)	14(11.6)	
+++	17(43.6)	37(30.6)	
KI67,n(%)			0.615
-	3(6.1)	5(3.5)	
+	5(10.2)	24(16.7)	
++	15(30.6)	39(27.1)	
+++	26(53.1)	76(52.8)	
Her2,n(%)			0.494
-	26(54.2)	76(62.3)	
+/-	2(4.2)	2(1.6)	
+	10(20.8)	26(21.3)	
++	6(12.5)	7(5.7)	
+++	4(8.3)	11(9.0)	
EGFR,n(%)			0.530
-	9(36.0)	19(37.3)	
+/-	0(0.0)	3(5.9)	
+	16(64.0)	28(54.9)	
++	0(0.0)	1(2.0)	

1.579 ; 95% confidence interval (CI), 1.150-2.168 ; p = .005) and the high PLR (PLR ≥ 107.7 ; HR, 1.590 ; 95% CI, 1.019-2.481 ; p = .041) were independent prognostic factors. (Table 2)(Figure 1)

Discussion

Researches have shown that systemic inflammation is associated with the prognosis of cancers (9,11,12). Inflammation has been proved to be a crucial and essential process in the development and progression of malignancies (5,7). SIR is associated with the outcome of a variety of cancers (13). It has been suggested that neutrophils, platelets, lymphocytes and monocytes play prominent roles in tumor-related inflammation and immunology (14,15). According to this, several inflammatory markers in blood have been studied in various malignant tumors. NLR, PLR and LMR are

Table 4. — **The correlation between PLR and clinicopathological features**

	PLR		
Clinicopathological features	**<107.7**	**>=107.7**	**P value**
Age,n(%)			0.374
<65	30(73.2)	174(66.2)	
>=65	11(26.8)	89(33.8)	
Gender,n(%)			0.419
Male	29(70.7)	169(64.3)	
Female	12(29.3)	94(35.7	
Primary site of tumor,n(%)			0.546
Upper	6(14.6)	45(17.3)	
Middle	19(46.3)	114(43.8)	
Lower	16(39.0)	90(34.6)	
Leather stomach	0(0)	11(4.2)	
Differentiation,n(%)			0.619
Medium diff G2	3(11.5)	19(15.4)	
Poorly diff G3	23(88.5)	101(82.1)	
Undiff G4	0(0)	3(2.4)	
Systemic chemotherapy, n(%)			0.501
No	6(14.6)	50(19.0)	
Yes	35(85.4)	213(81.0)	
Anemia,n(%)			0.076
Hb>=110(g/L)	31(75.6)	161(61.2)	
Hb<110(g/L)	10(24.4)	102(38.8)	
Jaundice,n(%)			0.013
TBil:1.7-17.1(μmol/L)	29(72.5)	231(89.2)	
TBil:17.1-34.2(μmol/L)	9(22.5)	24(9.3)	
TBil >34.2(μmol/L)	2(5.0)	4(1.5)	
Hypoproteinemia,n(%)			0.456
Alb>=35.0(g/L)	34(85.0)	208(80.0)	
Alb<35.0(g/L)	6(15.0)	52(20.0)	
P53,n(%)			0.716
-	5(25.0)	47(33.6)	
+	4(20.0)	31(22.1)	
++	2(10.0)	17(12.1)	
+++	9(45.0)	45(32.1)	
KI67,n(%)			0.126
-	2(8.7)	6(3.5)	
+	1(4.3)	28(16.5)	
++	4(17.4)	50(29.4)	
+++	16(69.6)	86(50.6)	
Her2,n(%)			0.002
-	14(58.3)	88(60.3)	
+/-	3(12.5)	1(0.7)	
+	2(8.3)	34(23.3)	
++	1(4.2)	12(8.2)	
+++	4(16.7)	11(7.5)	
EGFR,n(%)			0.861
-	4(36.4)	24(36.9)	
+/-	0	3(4.6)	
+	7(63.6)	37(56.9)	
++	0(0.0)	1(1.5)	

three markers that present enormous potential (15,16). Regarding previous studies, we presently deemed the usefulness of the application of NLR, PLR and LMR values in GC (17-20). Whether there is a correlation between systemic inflammation markers in stage IV GC and their prognostic value has remained unclear.

In this analysis of 304 stage IV GC patients, systemic inflammatory markers, measured as the NLR and PLR, were proven to be independent predictors of OS for patients with stage IV GC. High NLR and PLR values both indicate poor OS. LMR did not show significant indication to OS of stage IV GC. Among Clinicopathological features, systemic chemotherapy and jaundice were proven to be independent predictors of OS for patients with stage IV GC. Systemic chemotherapy shows a clear OS benefit in patients with stage IV GS.

Table 5. — **The correlation between LMR and clinicopathological features**

	LMR		
Clinicopathological features	**<5.2**	**>=5.2**	**P value**
Age,n(%)			0.629
<65	180(66.7)	22(71.0)	
>=65	90(33.3)	9(29.0)	
Gender,n(%)			<0.001
Male	186(68.9)	9(29.0)	
Female	84(31.1)	22(71.0)	
Primary site of tumor,n(%)			0.054
Upper	50(18.7)	1(3.2)	
Middle	111(41.6)	20(64.5)	
Lower	96(36.0)	9(29.0)	
Leather stomach	10(3.7)	1(3.2)	
Differentiation,n(%)			0.445
Medium diff G2	20(15.5)	1(5.9)	
Poorly diff G3	106(82.2)	16(94.1)	
Undiff G4	3(2.3)	0(0.0)	
Systemic chemotherapy, n(%)			0.910
No	50(18.5)	6(19.4)	
Yes	220(81.5)	25(80.6)	
Anemia,n(%)			0.320
Hb>=110(g/L)	167(61.9)	22(71.0)	
Hb<110(g/L)	103(38.1)	9(29.0)	
Jaundice,n(%)			0.489
TBil:1.7-17.1(μmol/L)	229(86.4)	29(93.5)	
TBil:17.1-34.2(μmol/L)	31(11.7)	2(6.5)	
TBil >34.2(μmol/L)	5(1.9)	0(0.0)	
Hypoproteinemia,n(%)			0.325
Alb>=35.0(g/L)	212(79.7)	27(87.1)	
Alb<35.0(g/L)	54(20.3)	4(12.9)	
P53,n(%)			0.326
-	44(30.3)	7(50.0)	
+	33(22.8)	3(21.4)	
++	19(13.1)	0(0.0)	
+++	49(33.8)	4(28.6)	
KI67,n(%)			0.053
-	7(4.0)	1(6.3)	
+	23(13.1)	6(37.5)	
++	52(29.7)	2(12.5)	
+++	93(53.1)	7(43.8)	
Her2,n(%)			0.517
-	90(60.0)	11(61.1)	
+/-	3(2.0)	1(5.6)	
+	30(20.0)	5(27.8)	
++	12(8.0)	1(5.6)	
+++	15(10.0)	0(0.0)	
EGFR,n(%)			0.434
-	24(35.8)	4(50.0)	
+/-	2(3.0)	1(12.5)	
+	40(59.7)	3(37.5)	
++	1(1.5)	0(0.0)	

Jaundice indicates poor OS. The metastasis site and the number of metastasis sites did not show significant indication to OS of stage IV GC (Figure 1).

The NLR is a highly reproducible, cost-effective and widely available prognostic marker for GC patients (8,21,22). It has been shown that a high level of NLR predicted poor outcome of GC patients (8,23). Furthermore, studies have indicated that the NLR is a useful predictive marker in advanced GC patients treated with adjuvant chemotherapy (8). PLR qualifies as a prognostic indicator for patients with GC treated with neoadjuvant chemotherapy. Low PLR may help clinicians identify those patients who will benefit from neoadjuvant chemotherapy (24). Recent evidence indicates that lymphocytes can enhance cancer immune-surveillance to inhibit tumor cell proliferation, invasion, and metastasis

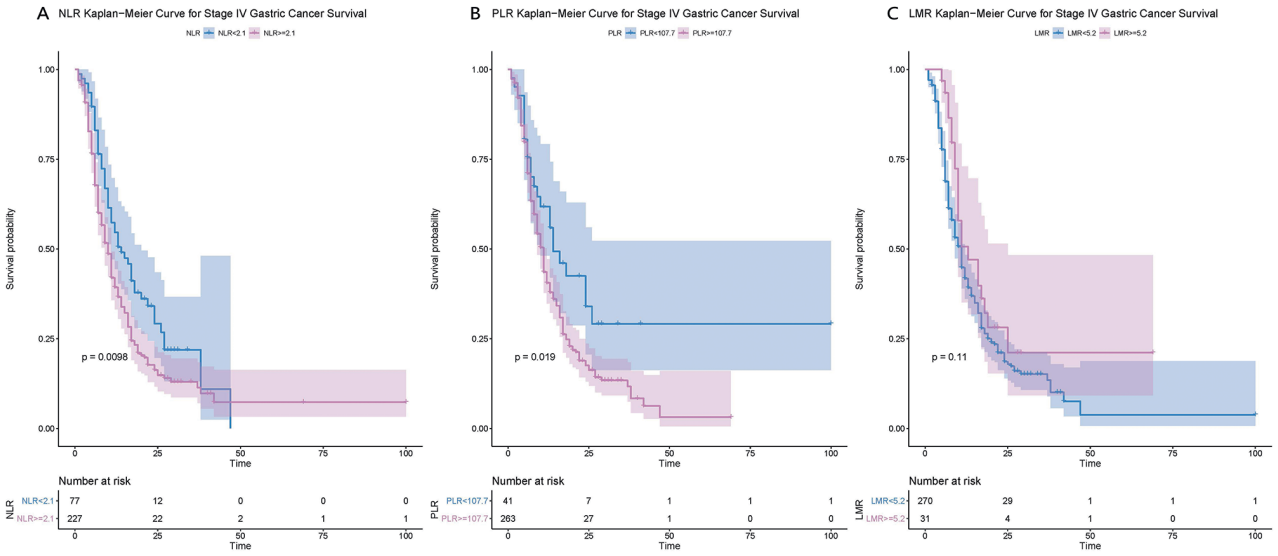

Fig. 1. — Kaplan-Meier analysis for overall survival (OS) of patients with stage IV GC according to the "Peritoneal metastasis", "Liver metastasis", and "Number of metastatic sites" ("1 versus >=2" and "1, 2 versus >=3"). Kaplan-Meier analysis for OS according to (A) Peritoneal metastasis, (B) Liver metastasis, (C) Number of metastatic sites : 1 versus >=2, (D) Number of metastatic sites : 1, 2 versus >=3.

(25). It was found that the presence of tumor-infiltrating lymphocytes was associated with improved outcomes in a variety of cancers, possibly owing to tumor-infiltrating, lymphocyte-induced, antitumor activity and inhibition of angiogenesis (26). Circulating monocytes may contribute to both tumor growth and reduced immunosurveillance, which is supported by previous findings (27).

X-tile plot is a novel time-dependent cutoff value analysis based on survival information, which identifies the cutoff value with minimum p values from log-rank $\chi 2$ statistics for the categorical biomarkers in terms of survival, which has been widely used in previous studies (28,29). Therefore, in our study, the other optimal cutoff values for the inflammatory biomarkers were calculated by the software.

This study was not without limitations. Because of the short OS of the stage IV GC, it is difficult to have a significant difference in the systemic immune status and clinical features on the OS. However, the markers that reflect the difference is thus valuable. As retrospective research, this study must have selection bias. There may be inevitable confounding factors in the study, such as socioeconomic status, diet, and alcohol consumption, which could pose an influence on NLR, PLR and LMR. Other markers of systemic inflammation like C-reactive protein and interleukin were not concluded in this research because of the low total detection rate. Adenocarcinoma of the stomach was histologically confirmed by endoscopy or resection. However, for the author, endoscopic pathological analyses can only be obtained from paper history. So there was a lack of pathologic data.

Conclusions

In conclusion, the NLR and PLR showed their potential usage in the prognosis of stage IV GC. SIR markers are reproducible, cost-effective and widely available prognostic markers. However, other inflammatory condition and the limitation of this study may affect the result. Therefore, the use of these parameters in predicting the OS of stage IV GC warrants for a more comprehensive and prospective research study before further implementation in clinical settings.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

Chen Huang and Zhaoyan Li conceived the study. Aiguang Zhao, Zizhen Zhang, Xiang Xia and Danhua Xu participated in study design. Chen Huang and Zhaoyan Li collected the data. Chen Huang performed statistical analyses. Chen Huang and Zhaoyan Li drafted the manuscript. Gang Zhao edited and checked the manuscript. All of the authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the ethics committee of Shanghai Jiaotong University of medicine, Renji Hospital Ethics Committee (No. 2017-114)

Competing interests

The authors declare that they have no competing interests.

References

1. BRAY F, FERLAY J, SOERJOMATARAM I, SIEGEL RL, TORRE LA, JEMAL A. Global cancer statistics 2018 : globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin*., 2018, **68** : 394-424.
2. SASAKO M, SANO T, YAMAMOTO S, KUROKAWA Y, NASHIMOTO A, KURITA A, HIRATSUKA M, TSUJINAKA T, KINOSHITA T, ARAI K, YAMAMURA Y, OKAJIMA K. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N. Engl. J. Med*., 2008, **359** : 453-462.
3. LIU K, YANG K, WU B, CHEN H, CHEN X, CHEN X, JIANG L, YE F, HE D, LU Z, XUE L, ZHANG W, LI Q, ZHOU Z, MO X, HU J. Tumor-infiltrating immune cells are associated with prognosis of gastric cancer. *Medicine (Baltimore)*, 2015, **94** : e1631.
4. STOTZ M, PICHLER M, ABSENGER G, SZKANDERA J, ARMINGER F, SCHABERL-MOSER R, SAMONIGG H, STOJAKOVIC T, GERGER A. The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage iii colon cancer. *Br. J. Cancer*, 2014, **110** : 435-440.
5. KILINCALP S, EKIZ F, BASAR O, AYTE MR, COBAN S, YILMAZ B, ALTINBAS A, BASAR N, AKTAS B, TUNA Y, ERBIS H, UCAR E, ERARSLAN E, YUKSEL O. Mean platelet volume could be possible biomarker in early diagnosis and monitoring of gastric cancer. *Platelets*, 2014, **25** : 592-594.
6. ILHAN N, ILHAN N, ILHAN Y, AKBULUT H, KUCUKSU M. C-reactive protein, procalcitonin, interleukin-6, vascular endothelial growth factor and oxidative metabolites in diagnosis of infection and staging in patients with gastric cancer. *World J. Gastroenterol*., 2004, **10** : 1115-1120.
7. KIM DK, OH SY, KWON HC, LEE S, KWON KA, KIM BG, KIM SG, KIM SH, JANG JS, KIM MC, KIM KH, HAN JY, KIM HJ. Clinical significances of preoperative serum interleukin-6 and c-reactive protein level in operable gastric cancer. *BMC Cancer*, 2009, **9** : 155.
8. LEE S, OH SY, KIM SH, LEE JH, KIM MC, KIM KH, KIM HJ. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with folfox chemotherapy. *BMC Cancer*, 2013, **13** : 350.
9. DIAKOS CI, CHARLES KA, MCMILLAN DC, CLARKE SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*., 2014, **15** : e493-e503.
10 CAMP RL, DOLLED-FILHART M, RIMM DL. X-tile : a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin. Cancer Res*., 2004, **10** : 7252-7259.
11 HSU JT, WANG CC, LE PH, CHEN TH, KUO CJ, LIN CJ, CHOU WC, YEH TS. Lymphocyte-to-monocyte ratios predict gastric cancer surgical outcomes. *J. Surg. Res*., 2016, **202** : 284-290.
12 WANG SL, ZHUANG CL, HUANG DD, PANG WY, LOU N, CHEN FF, ZHOU CJ, SHEN X, YU Z. Sarcopenia adversely impacts postoperative clinical outcomes following gastrectomy in patients with gastric cancer : a prospective study. *Ann. Surg. Oncol*., 2016, **23** : 556-564.
13 CARRUTHERS R, THO LM, BROWN J, KAKUMANU S, MCCARTNEY E, MCDONALD AC. Systemic inflammatory response is a predictor of outcome in patients undergoing preoperative chemoradiation for locally advanced rectal cancer. *Colorectal Dis*., 2012, **14** : e701-e707.
14 SCHREIBER RD, OLD LJ, SMYTH MJ. Cancer immunoediting : integrating immunity's roles in cancer suppression and promotion. *Science*, 2011, **331** : 1565-1570.
15 DUNN GP, OLD LJ, SCHREIBER RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity*, 2004, **21** : 137-148.
16 KEMAL Y, YUCEL I, EKIZ K, DEMIRAG G, YILMAZ B, TEKER F, OZDEMIR M. Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. *Asian Pac. J. Cancer Prev*., 2014, **15** : 2651-2654.
17 MIYAMOTO R, INAGAWA S, SANO N, TADANO S, ADACHI S, YAMAMOTO M. The neutrophil-to-lymphocyte ratio (nlr) predicts short-term and long-term outcomes in gastric cancer patients. *Eur. J. Surg. Oncol*., 2018, **44** : 607-612.
18 LI Y, WANG C, XU M, KONG C, QU A, ZHANG M, ZHENG Z, ZHANG G. Preoperative nlr for predicting survival rate after radical resection combined with adjuvant immunotherapy with cik and postoperative chemotherapy in gastric cancer. *J. Cancer Res. Clin. Oncol*., 2017, **143** : 861-871.
19 LI S, XU X, LIANG D, TIAN G, SONG S, HE Y. Prognostic value of blood neutrophil-to-lymphocyte ratio (nlr) and platelet-to-lymphocyte ratio (plr) in patients with gastric cancer. *Zhonghua Zhong Liu Za Zhi*, 2014, **36** : 910-915.
20 PAN YC, JIA ZF, CAO DH, WU YH, JIANG J, WEN SM, ZHAO D, ZHANG SL, CAO XY. Preoperative lymphocyte-to-monocyte ratio (lmr) could independently predict overall survival of resectable gastric cancer patients. *Medicine (Baltimore)*, 2018, **97** : e13896.
21 SHIMADA H, TAKIGUCHI N, KAINUMA O, SODA H, IKEDA A, CHO A, MIYAZAKI A, GUNJI H, YAMAMOTO H, NAGATA M. High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. *Gastric Cancer*, 2010, **13** : 170-176.
22 YAMANAKA T, MATSUMOTO S, TERAMUKAI S, ISHIWATA R, NAGAI Y, FUKUSHIMA M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. *Oncology*, 2007, **73** : 215-220.
23 SUN J, CHEN X, GAO P, SONG Y, HUANG X, YANG Y, ZHAO J, MA B, GAO X, WANG Z. Can the neutrophil to lymphocyte ratio be used to determine gastric cancer treatment outcomes? A systematic review and meta-analysis. *Dis. Markers*, 2016 : 7862469.
24 CHEN L, HAO Y, CONG X, ZOU M, LI S, ZHU L, SONG H, XUE Y. Peripheral venous blood platelet-to-lymphocyte ratio (plr) for predicting the survival of patients with gastric cancer treated with sox or xelox regimen neoadjuvant chemotherapy. *Technol. Cancer Res. Treat*., 2019, **18** : 1078097133.
25 DUNN GP, OLD LJ, SCHREIBER RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity*, 2004, **21** : 137-148.
26 AZIMI F, SCOLYER RA, RUMCHEVA P, MONCRIEFF M, MURALI R, MCCARTHY SW, SAW RP, THOMPSON JF. Tumor-infiltrating lymphocyte grade is an independent predictor of sentinel lymph node status and survival in patients with cutaneous melanoma. *J. Clin. Oncol*., 2012, **30** : 2678-2683.
27 AUGIER S, CIUCCI T, LUCI C, CARLE GF, BLIN-WAKKACH C, WAKKACH A. Inflammatory blood monocytes contribute to tumor development and represent a privileged target to improve host immunosurveillance. *J. Immunol*., 2010, **185** : 7165-7173.
28 ZHENG ZF, LU J, ZHENG CH, LI P, XIE JW, WANG JB, LIN JX, CHEN QY, LIN M, HUANG CM. A novel prognostic scoring system based on preoperative sarcopenia predicts the long-term outcome for patients after r0 resection for gastric cancer : experiences of a high-volume center. *Ann. Surg. Onco*l., 2017, **24** : 1795-1803.
29 QURESHI YA, SARKER SJ, WALKER RC, HUGHES SF. Proximal resection margin in ivor-lewis oesophagectomy for cancer. *Ann. Surg. Oncol*., 2017, **24** : 569-577.