



Retrospective Cohort Study

## Absolute monocyte and lymphocyte count prognostic score for patients with gastric cancer

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**Author contributions:** Kim A and Kim HY carried out a role as co-corresponding authors equally; Eo WK and Kim HY designed the research; Choi SI performed Patient Recruitment; Jeong DW and Chang HJ performed data collection; Won KY and Kim YO performed data interpretation as responsible pathologists; Oh YL, Lee TH, Kim KH, Ji YI and Kim A analyzed the data and reviewed manuscript; Kim SH performed statistical analysis; Eo WK and Chun SW wrote the paper.

**Supported by** Kyung Hee University in 2006, No. KHU-20061216.

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Received: August 19, 2014

Peer-review started: August 20, 2014

First decision: September 27, 2014

Revised: October 16, 2014

Accepted: December 5, 2014

Article in press: December 8, 2014

Published online: March 7, 2015

### Abstract

**AIM:** To measure the prognostic significance of absolute monocyte count/absolute lymphocyte count prognostic score (AMLPS) in patients with gastric cancer.

**METHODS:** We retrospectively examined the combination of absolute monocyte count (AMC) and absolute lymphocyte count (ALC) as prognostic variables in a cohort of 299 gastric cancer patients who underwent surgical resection between 2006 and 2013 and were followed at a single institution. Both AMC and ALC were dichotomized into two groups using cut-off points determined by receiving operator characteristic curve analysis. An AMLPS was generated, which stratified patients into three risk groups: low risk (both low AMC and high ALC), intermediate risk (either high AMC or low ALC), and high risk (both high AMC and low ALC). The primary objective of the study was to validate the impact of AMLPS on both disease-free survival (DFS) and overall survival (OS), and the second objective was to assess the AMLPS as an independent prognostic factor for survival in comparison with known prognostic factors.

**RESULTS:** Using data from the entire cohort, the most discriminative cut-off values of AMC and ALC selected on the receiver operating characteristic curve were 672.4/ $\mu\text{L}$  and 1734/ $\mu\text{L}$  for DFS and OS. AMLPS risk groups included 158 (52.8%) patients in the low-risk, 128 (42.8%) in the intermediate-risk, and 13 (4.3%) in the high-risk group. With a median follow-up of 37.2 mo (range: 1.7-91.4 mo), five-year DFS rates in the low-, intermediate-, and high-risk groups were 83.4%, 78.7%, and 19.8%, respectively. And five-year OS rates in the low-, intermediate-, and high-risk groups were 89.3%, 81.1%, and 14.4%, respectively. On multivariate analysis performed with patient- and tumor-related factors, we identified AMLPS, age, and pathologic tumor-node-metastasis stage as the most valuable prognostic factors impacting DFS and OS.

**CONCLUSION:** AMLPS identified patients with a poor DFS and OS, and it was independent of age, pathologic stage, and various inflammatory markers.

**Key words:** Monocytes; Absolute lymphocyte count; Stomach neoplasms

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**Core tip:** Our findings suggest that the absolute monocyte count (AMC) and absolute lymphocyte count (ALC) prognostic score combined by AMC and ALC can predict survival and identify gastric cancer patients with a poor overall survival, and this prognostic score is independent of age, pathologic stage, and various inflammatory markers.

Eo WK, Jeong DW, Chang HJ, Won KY, Choi SI, Kim SH, Chun SW, Oh YL, Lee TH, Kim YO, Kim KH, Ji YI, Kim A, Kim HY. Absolute monocyte and lymphocyte count prognostic score for patients with gastric cancer. *World J Gastroenterol* 2015; 21(9): 2668-2676 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i9/2668.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i9.2668>

## INTRODUCTION

Gastric cancer is a major public health problem, because it represents one of the major causes of cancer mortality worldwide. Despite a result of advances in surgical treatment, the role of surgery as mainstay treatment is limited to around a quarter of all patients<sup>[1]</sup>, and overall survival (OS) of patients who undergo surgery progressively diminishes as stage increases, ranging from 75% for stage I to 35% or less for stage II and beyond<sup>[2]</sup>; accurately predicting patients' prognoses is needed to improve patient survival and to provide important information to the patients.

After curative resection for gastric cancer, pathologic analysis of tumor-related factors guides prognosis and

treatment. A variety of high-risk features, including tumor stage, resection margin, and nodal status, are considered to be important in determining cancer recurrence and survival<sup>[3]</sup>. In addition, a few serum tumor markers have been found to be associated with poor prognosis and are therefore useful for monitoring and predicting early recurrence and poor prognosis<sup>[4]</sup>. The outcomes of patients with cancer are determined not only by tumor-related factors but also by host-related factors, particularly the systemic inflammatory response<sup>[5,6]</sup>. Laboratory markers of systemic inflammation have been investigated as both prognostic and predictive biomarkers in several cancer populations. With respect to gastric cancer, the modified Glasgow Prognostic Score<sup>[7]</sup>, mean platelet volume (MPV)<sup>[8]</sup>, absolute neutrophil count (ANC)<sup>[9]</sup>, absolute monocyte counts (AMC)<sup>[9]</sup>, absolute lymphocyte count (ALC)<sup>[9]</sup>, neutrophil-lymphocyte ratio (NLR)<sup>[10-13]</sup>, and platelet-lymphocyte ratio (PLR)<sup>[12]</sup> have been reported as independent prognostic factors in gastric cancer. Assessment of the inflammatory response to the tumor may be easier and more-cost effective in clinical practice, and the addition of inflammatory factors to tumor-associated factors would be expected to help in disease management.

Recently, the role of monocytes in combination with peripheral lymphocytes has been assessed as a biomarker in lymphomas. In some of those reports, each AMC and ALC was divided into two to create a prognostic index, and it was shown to be an independent prognostic factor for survival in diffuse large B-cell lymphoma (DLBCL)<sup>[14-18]</sup>. However, to our knowledge, there is limited data available on whether such a prognostic index at diagnosis has prognostic value in other malignancies, including gastric cancer. Therefore, the aim of the present study is to measure the prognostic significance of a preoperative combination of AMC and ALC by using this prognostic index in a cohort of patients with resectable primary gastric cancer.

## MATERIALS AND METHODS

We retrospectively evaluated 299 patients undergoing potentially curative resection of gastric cancer in a single institution between June 2006 and April 2013. No patient refused authorization to use his or her medical records for research. No patients were lost to follow-up. Approval for the retrospective review of these records was obtained from the Kyung Hee University Hospital at Gangdong Institutional Review Board (IRB file number 2014-02-027), and it was performed in accordance with Korean regulations and the Declaration of Helsinki.

Information regarding patient demographics was collected for analysis. Laboratory measurements, including complete blood counts (CBCs) and biochemical profiles, were performed within seven days before surgery as part of the routine workup.

Venous peripheral blood samples for measurement of CBCs were drawn just before the operation to avoid any inflammatory effects of preoperative sequential evaluation, such as gastroscopy, colonoscopy, or esophagogastroduodenoscopy. If several preoperative CBCs were obtainable, the one which was examined on the nearest date before the operation was taken. Two milliliters of venous blood were collected into tubes containing dipotassium ethylenedinitrotetra-acetic acid (EDTA), and all measurements were performed within 30 min after blood collection on a standard Coulter counter model LH 750 (Beckman Coulter Inc., CA, United States).

The tumors were staged according to the tumor-node-metastasis (TNM) criteria from the 7<sup>th</sup> edition of the International Union Against Cancer's classification of malignant tumors<sup>[19]</sup>. Patients were treated with curative surgical resection with D2 lymphadenectomy. All resections were conducted by a specialized gastric cancer surgeon who routinely operates on more than 50 new cases per year and who has two or more consecutive years of surgical practice. Those who had concurrent second malignancies or prior malignancies within the previous five years (other than *in situ* or non-melanoma skin cancers) were excluded. Those who had received neoadjuvant chemotherapy or who received a blood product transfusion within one month before resection were also excluded to avoid possible effects of such treatments on preoperative laboratory profiles. Patients were excluded if they were human immunodeficiency virus-positive, had evidence of infection, or had concomitant autoimmune disease treated with immunosuppressive therapies affecting their ALC and AMC values.

AMC and ALC were obtained from a standard complete blood count and a differential count was performed manually. Each AMC and ALC was divided into two groups (high and low) by using cut-off points determined by receiver operating characteristic (ROC) curve analysis for survival, and the prognostic index, AMC/ALC prognostic score (AMLPS), was generated. The AMLPS stratified patients into three risk groups: low risk (both low AMC and high ALC), intermediate risk (either high AMC or low ALC), and high risk (both high AMC and low ALC).

The primary objective of the study was to validate the impact of AMLPS on both disease-free survival (DFS) and OS. The second objective was to assess the AMLPS as an independent prognostic factor for survival in comparison with known prognostic factors. The following prognostic factors were evaluated in this study: age, gender, tumor size, TNM stage, lymphatic or vascular invasion, serum albumin concentration, AMC, ALC, hemoglobin concentration, platelet count, MPV, NLR, PLR, and AMLPS.

DFS was defined as the time (in months) from the date of surgery to the date of relapse, death from any cause, or last follow-up. OS was defined as the time (in months) from the date of surgery to the date of death

from any cause or last follow-up. Patients without relapse or death were censored at time of the last known follow-up.

### Statistical analysis

*P* values for the comparison of the mean difference for continuous variables were obtained by using analysis of variance (ANOVA) with post-hoc pairwise comparisons (Scheffe's test); *P* values from an independent test for categorical variables were obtained by using a  $\chi^2$  test. OS was analyzed using the Kaplan-Meier method. Differences between survival curves were tested for statistical significance using a two-tailed log-rank test. The Cox proportional hazards model was used for univariate analysis. Variables with a *P* value < 0.05 in the univariate analysis were included in the multivariate analysis. The multivariate Cox proportional hazards model was used to identify the most valuable prognostic factors affecting survival. All *P* values presented are two-sided and statistical significance was declared at *P* < 0.05. Data were analyzed using SPSS statistical software (version 18.0, SPSS Inc., Chicago, Ill., United States).

## RESULTS

Baseline characteristics of the patients are displayed in Tables 1 and 2. The median age at diagnosis was 59 years (range: 25-92 years). Male patients comprised 65.2% of the subjects in this study. Tubular adenocarcinoma was diagnosed in 62.5% of the patients. The median longitudinal tumor diameter was 3.0 cm (range: 0.2-20.0 cm). The most frequent location of the tumor was in the lower third of the stomach (58.9%). Stage I, II, and III disease comprised 59.9%, 20.1%, and 20.1% of the cases, respectively. The median AMC and ALC at diagnosis were 458.2/ $\mu$ L (range: 31.0-1618.5/ $\mu$ L) and 1879.2/ $\mu$ L (range: 341.0-5271.7/ $\mu$ L), respectively. The median hemoglobin concentration was 13.1 g/dL (range: 5.7-17.9 g/dL). The median platelet count and MPV were 235000/ $\mu$ L (range: 54000-577000/ $\mu$ L) and 7.8 fL (range: 5.9-10.9 fL), respectively. The median NLR and PLR were 2.0 (range: 0.4-25.6) and 122.5 (range: 34.3-1190.6), respectively. The median serum albumin concentration was 4.1 g/dL (range: 2.4-5.1 g/dL).

Using data from the entire cohort, we selected cut-off points for the AMC and ALC to predict the survival outcomes from the ROC curve analysis. The most discriminative cut-off values of AMC and ALC on the ROC curve were 672.4/ $\mu$ L (sensitivity 23.08, specificity 89.88, AUC 0.560, *P* = 0.1791) and 1734/ $\mu$ L (sensitivity 59.62, specificity 65.18, AUC 0.602, *P* = 0.0253), respectively, for DFS. In terms of OS, the most discriminative cut-off values of AMC and ALC on the ROC curve were 672.4/ $\mu$ L (sensitivity 26.19, specificity 89.88, AUC 0.577, *P* = 0.1189) and 1734/ $\mu$ L (sensitivity 64.29, specificity 64.98, AUC 0.625, *P* = 0.0129), respectively.

**Table 1 Demographics and tumor-related factors in patients with gastric cancer *n* (%)**

Variable	
Median age (range, yr)	59 (25-92)
Male: female	195:104 (65.2:34.8)
Lauren's classification	
Intestinal	148 (49.5)
Diffuse	79 (26.4)
Mixed	58 (19.4)
Unknown	14 (4.7)
Median tumor size (range), cm	3.0 (0.2-20.0)
Location	
Upper1/3	28 (9.4)
Mid1/3	90 (30.1)
Lower1/3	176 (58.9)
Diffuse	5 (1.7)
Lymphatic invasion	
Negative	203 (67.9)
Positive	96 (32.1)
Vascular invasion	
Negative	287 (96.0)
Positive	12 (4.0)
T category	
T1	168 (56.2)
T2	29 (9.7)
T3	73 (24.4)
T4	29 (9.7)
N category	
N0	199 (66.6)
N1	39 (13.0)
N2	25 (8.4)
N3	36 (12.0)
TNM stage	
I	179 (59.9)
II	60 (20.1)
III	60 (20.1)

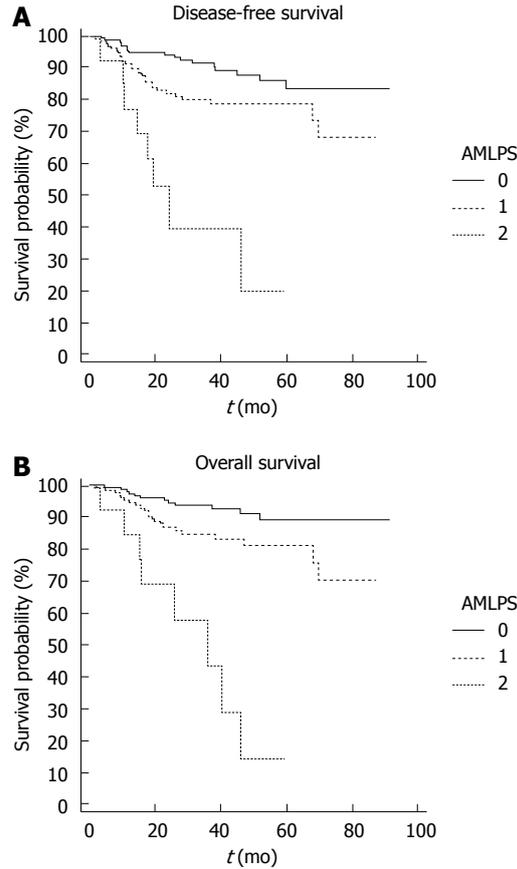
TNM: Tumor node metastasis.

**Table 2 Host-related factors in patients with gastric cancer**

Variable	Mean ± SD	Median (range)
WBC (/μL)	6857.5 ± 2358.8	6500.0 (1900.0-19500.0)
ANC (/μL)	4180.8 ± 2054.4	3718.4 (1064.0-17100.0)
AMC (/μL)	480.6 ± 180.1	458.2 (31.0-1618.5)
ALC (/μL)	1980.8 ± 633.9	1879.2 (341.0-5271.7)
Hemoglobin (g/dL)	12.8 ± 2.2	13.1 (5.7-17.9)
MCV (fL)	91.6 ± 7.5	92.8 (56.7-109.4)
Platelet (× 10 <sup>3</sup> /μL)	245.4 ± 71.8	235 (54.0-577.0)
MPV (fL)	7.9 ± 0.8	7.8 (5.9-10.9)
NLR	2.4 ± 1.9	2.0 (0.4-25.6)
PLR	138.0 ± 85.8	122.5 (34.3-1190.6)
Albumin (g/dL)	4.1 ± 0.4	4.1 (2.4-5.1)

SD: Standard deviation; ANC: Absolute neutrophil count; AMC: Absolute monocyte count; ALC: Absolute lymphocyte count; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte count ratio; PLR: Platelet/lymphocyte count ratio.

Either AMC or ALC as a single parameter appeared to have a limited ability to identify patients in the poor-risk category. Therefore, we combined the baseline AMC with the baseline ALC as dichotomized variables to obtain a host immunity-related prognostic index of survival, AMLPS, in patients with gastric cancer. We



**Figure 1 Absolute monocyte count/absolute lymphocyte count prognostic score predict the disease-free survival (A) and overall survival (B) in patients with gastric cancer. AMLPS: 0, low-risk; 1, intermediate-risk; 2, high-risk. AMLPS: absolute monocyte count/absolute lymphocyte count prognostic score.**

stratified patients into three risk groups depending on the AMLPS: low-risk (both AMC ≤ 672.4/μL and ALC > 1734/μL), intermediate-risk (either AMC > 672.4/μL or ALC ≤ 1734/μL) and high-risk (both AMC > 672.4/μL and ALC ≤ 1734/μL). AMLPS risk groups included 158 (52.8%) patients in the low-, 128 (42.8%) in the intermediate-, and 13 (4.3%) in the high-risk groups.

In order to evaluate the relevance of the AMLPS, we compared the different categories of AMLPS with the baseline characteristics. The variables used for the ANOVA analysis showed normal distribution. Significant mean differences between the low- and high-risk groups were obtained for the following continuous variables: tumor size, serum albumin concentration, AMC, ALC, hemoglobin concentration, NLR, and PLR. Whereas, significant mean differences for categorical variables were obtained for pathologic T category, pathologic TNM stage, and vascular invasion (Table 3).

With a median follow-up of 37.2 mo (range: 1.7-91.4 mo), AMLPS had significant effects on survival rates: five-year DFS rates in the low-, intermediate-, and high-risk groups were 83.4%, 78.7%, and 19.8%, respectively, and five-year OS rates in the low-, intermediate-, and high-risk groups were 89.3%, 81.1%, and 14.4%, respectively (Figure 1).

Univariate analysis for DFS identified a significant

**Table 3** Clinical characteristics according to the absolute monocyte count/absolute lymphocyte count prognostic score in patients with gastric cancer

Variable	Low risk (n = 158) <sup>4</sup>		Intermediate risk (n = 128) <sup>4</sup>		High risk (n = 13) <sup>4</sup>		P value
	n (%)	Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD	
Age (yr)		56.4 ± 10.7 <sup>1</sup>		61.2 ± 12.2 <sup>2</sup>		64.0 ± 10.1 <sup>1,2</sup>	0.0006
Gender							0.2602
Male	99 (62.7)		85 (66.4)		11 (84.6)		
Female	59 (37.3)		43 (33.6)		2 (15.4)		
Tumor size (cm)		3.7 ± 2.9 <sup>1</sup>		4.3 ± 3.2 <sup>1</sup>		7.1 ± 5.1 <sup>2</sup>	0.0005
T category							0.0008
T1-2	117 (74.1)		76 (59.4)		4 (30.8)		
T3-4	41 (25.9)		52 (40.6)		9 (69.2)		
N category							0.0565
N0	111 (70.3)		83 (64.8)		5 (38.5)		
N1-3	47 (29.7)		45 (35.2)		8 (61.5)		
TNM stage							0.0200
I - II	133 (84.2)		99 (77.3)		7 (53.8)		
III	25 (15.8)		29 (22.7)		6 (46.2)		
Lymphatic invasion							0.0102
Negative	117 (74.1)		81 (63.3)		5 (38.5)		
Positive	41 (25.9)		47 (36.7)		8 (61.5)		
Vascular invasion							0.0105
Negative	156 (98.7)		120 (93.8)		11 (84.6)		
Positive	2 (1.3)		8 (6.3)		2 (15.4)		
Albumin (g/dL)		4.2 ± 0.3 <sup>1</sup>		4.0 ± 0.4 <sup>2</sup>		3.7 ± 0.5 <sup>3</sup>	< 0.0001
AMC (/ $\mu$ L)		459.1 ± 110.0 <sup>1</sup>		478.3 ± 226.9 <sup>1</sup>		765.5 ± 93.9 <sup>2</sup>	< 0.0001
ALC (/ $\mu$ L)		2283.8 ± 423.1 <sup>1</sup>		1661.2 ± 685.9 <sup>2</sup>		1444.9 ± 219.5 <sup>2</sup>	< 0.0001
Hemoglobin (g/dL)		13.4 ± 1.9 <sup>1</sup>		12.4 ± 2.3 <sup>2</sup>		10.2 ± 2.5 <sup>3</sup>	< 0.0001
Platelet ( $\times 10^3$ / $\mu$ L)		248.8 ± 66.6 <sup>1</sup>		238.7 ± 78.0 <sup>1</sup>		270.1 ± 67.0 <sup>1</sup>	0.2219
MPV (fL)		8.0 ± 0.9 <sup>1</sup>		7.9 ± 0.8 <sup>1</sup>		7.6 ± 0.9 <sup>1</sup>	0.2373
NLR		1.7 ± 0.7 <sup>1</sup>		2.9 ± 2.6 <sup>2</sup>		4.2 ± 2.6 <sup>2</sup>	< 0.0001
PLR		111.8 ± 35.3 <sup>1</sup>		165.0 ± 116.3 <sup>2</sup>		191.6 ± 58.3 <sup>2</sup>	< 0.0001

<sup>1,2,3</sup>Means with the same letter are not significantly different; <sup>4</sup>AMLPS (AMC/ALC prognostic score) was defined as low-risk (both AMC  $\leq$  672.4/ $\mu$ L and ALC > 1734/ $\mu$ L), intermediate-risk (either AMC > 672.4/ $\mu$ L or ALC  $\leq$  1734/ $\mu$ L) and high-risk (both AMC > 672.4/ $\mu$ L and ALC  $\leq$  1734/ $\mu$ L). P values for comparison of mean difference for continuous variables were obtained by analysis of variance with post-hoc test of Scheffe; P values for independent test for categorical variables were obtained by  $\chi^2$  test. TNM: Tumor node metastasis; SD: Standard deviation; ANC: Absolute neutrophil count; AMC: Absolute monocyte count; ALC: Absolute lymphocyte count; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte count ratio; PLR: Platelet/lymphocyte count ratio.

difference for both continuous and categorical variables, including age, tumor size, T-category, N-category, TNM stage, lymphatic invasion, vascular invasion, serum albumin concentration, AMC, ALC, hemoglobin concentration, platelet count, MPV, NLR, PLR, and AMLPS (high- vs intermediate-risk groups, and high- vs low-risk groups) (Table 4). Using the multivariate Cox proportional hazards model, the only predictors for DFS were age (HR = 3.33; 95%CI: 1.50-7.40; P = 0.0032), TNM staging system (HR = 4.69; 95%CI: 2.15-10.24; P = 0.0001), AMLPS (high- vs intermediate-risk groups; HR = 0.23; 95%CI: 0.10-0.56; P = 0.0011), and AMLPS (high- vs low-risk groups; HR = 0.40; 95%CI: 0.18-0.90; P = 0.0274; Table 4).

Using univariate analysis for OS, significant differences for both continuous and categorical variables were obtained in the same variables as in DFS (Table 5). In the multivariate analysis, the only predictors for OS were age (HR = 2.34; 95%CI: 1.25-4.37; P = 0.0083), TNM staging system (HR = 5.53; 95%CI: 2.96-10.34; P < 0.0001), AMLPS (high- vs intermediate-risk groups; HR = 0.17; 95%CI: 0.06-0.45; P = 0.0004),

and AMLPS (high- vs low-risk groups; HR = 0.30; 95%CI: 0.13-0.71; P = 0.0057; Table 5).

## DISCUSSION

Approximately 30 years ago, Bruckner *et al*<sup>[9]</sup> reported that pretreatment ANC, AMC, and ALC are independent indicators of prognosis for patients with metastatic gastric cancer. In their report, the combination of ANC and ALC also predicted a noticeable difference in OS<sup>[9]</sup>. Since that report, the use of ANC and ALC as prognostic factors in gastric cancer has been validated, usually by combining the two values to determine the NLR<sup>[10-12]</sup>. In addition, the role of ALC in combination with platelet count has been reported<sup>[20,21]</sup>. On the other hand, the prognostic value of AMC in gastric cancer has not been validated to the best of our knowledge.

Recently, the AMC and ALC were combined to generate a score that was shown to be prognostic for survival in DLBCL<sup>[14-17]</sup>. Contrary to conventional prognostic indices, this scoring system does not incorporate patient and tumor characteristics, which

**Table 4 Relationship between clinicopathologic characteristics, the systemic inflammatory or immunologic response, and disease-free survival in gastric cancer**

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (yr)	3.32 (1.50-7.35)	0.0032	3.33 (1.50-7.40)	0.0032
Tumor size (cm)	4.92 (2.79-8.69)	< 0.0001		
T category (T1-2 vs T3-4)	7.26 (3.82-13.81)	< 0.0001		
N category (N0 vs N1-3)	5.16 (2.87-9.27)	< 0.0001		
TNM Stage ( I -II vs III)	8.93 (5.08-15.69)	< 0.0001	4.69 (2.15-10.24)	0.0001
Lymphatic invasion	3.63 (2.08-6.32)	< 0.0001		
Vascular invasion	2.96 (1.17-7.47)	0.0214		
Albumin (g/dL)	0.29 (0.16-0.51)	< 0.0001		
AMC (/μL)	2.06 (1.08-3.92)	0.0285		
ALC (/μL)	0.37 (0.21-0.64)	0.0004		
Hemoglobin (g/dL)	0.32 (0.19-0.56)	< 0.0001		
Platelet (× 10 <sup>3</sup> /μL)	2.45 (1.41-4.26)	0.0015		
MPV (fL)	0.38 (0.18-0.77)	0.0080		
NLR	2.18 (1.22-3.88)	0.0085		
PLR	2.94 (1.68-5.13)	0.0002		
AMLPS <sup>1</sup>				
High- vs intermediate-risk <sup>2</sup>	0.11 (0.05-0.26)	< 0.0001	0.23 (0.10-0.56)	0.0011
High- vs low-risk <sup>3</sup>	0.24 (0.11-0.52)	0.0004	0.40 (0.18-0.90)	0.0274

<sup>1</sup>AMLPS (AMC/ALC prognostic score) was defined as low-risk (both AMC ≤ 672.4/μL and ALC > 1734/μL), intermediate-risk (either AMC > 672.4/μL or ALC ≤ 1734/μL) and high-risk (both AMC > 672.4/μL and ALC ≤ 1734/μL); <sup>2</sup>Statistically significant after adjusting for age, tumor size, T category, N category, TNM stage, lymphatic invasion, vascular invasion, serum albumin concentration, hemoglobin concentration, platelet count, MPV, NLR, PLR, and low-risk AMLPS; <sup>3</sup>Statistically significant after adjusting for age, tumor size, T category, N category, TNM stage, lymphatic invasion, vascular invasion, serum albumin concentration, hemoglobin concentration, platelet count, MPV, NLR, PLR, and intermediate-risk AMLPS. Hazard ratio (HR) was obtained by Cox's proportional hazard model. TNM: Tumor node metastasis; AMC: Absolute monocyte count; ALC: Absolute lymphocyte count; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte count ratio; PLR: Platelet/lymphocyte count ratio.

**Table 5 Relationship between clinicopathologic characteristics, the systemic inflammatory or immunologic response, and overall survival in gastric cancer**

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (yr)	2.68 (1.46-4.92)	0.0016	2.34 (1.25-4.37)	0.0083
Tumor size (cm)	4.47 (2.38-8.37)	< 0.0001		
T category (T1-2 vs T3-4)	5.12 (2.63-9.98)	< 0.0001		
N category (N0 vs N1-3)	3.57 (1.92-6.64)	0.0001		
TNM Stage ( I -II vs III)	6.28 (3.41-11.55)	< 0.0001	5.53 (2.96-10.34)	< 0.0001
Lymphatic invasion	2.88 (1.56-5.28)	0.0007		
Vascular invasion	2.71 (0.97-7.63)	0.0583		
Albumin (g/dL)	0.27 (0.14-0.52)	0.0001		
AMC (/μL)	2.41 (1.21-4.79)	0.0125		
ALC (/μL)	0.31 (0.16-0.58)	0.0003		
Hemoglobin (g/dL)	0.40 (0.22-0.73)	0.0030		
Platelet (× 10 <sup>3</sup> /μL)	2.11 (1.14-3.93)	0.0188		
MPV (fL)	0.52 (0.28-0.97)	0.0415		
NLR	2.21 (1.17-4.19)	0.0155		
PLR	3.18 (1.70-5.97)	0.0003		
AMLPS <sup>1</sup>				
High- vs intermediate-risk <sup>2</sup>	0.08 (0.03-0.21)	< 0.0001	0.17 (0.06-0.45)	0.0004
High- vs low-risk <sup>3</sup>	0.20 (0.09-0.44)	< 0.0001	0.30 (0.13-0.71)	0.0057

<sup>1</sup>AMLPS (AMC/ALC prognostic score) was defined as low-risk (both AMC ≤ 672.4/μL and ALC > 1734/μL), intermediate-risk (either AMC > 672.4/μL or ALC ≤ 1734/μL) and high-risk (both AMC > 672.4/μL and ALC ≤ 1734/μL); <sup>2</sup>Statistically significant after adjusting for age, tumor size, T category, N category, TNM stage, lymphatic invasion, vascular invasion, serum albumin concentration, hemoglobin concentration, platelet count, MPV, NLR, PLR, and low-risk AMLPS; <sup>3</sup>Statistically significant after adjusting for age, tumor size, T category, N category, TNM stage, lymphatic invasion, vascular invasion, serum albumin concentration, hemoglobin concentration, platelet count, MPV, NLR, PLR, and intermediate-risk AMLPS. Hazard ratio (HR) was obtained by Cox's proportional hazard model. TNM: Tumor node metastasis; AMC: Absolute monocyte count; ALC: Absolute lymphocyte count; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte count ratio; PLR: Platelet/lymphocyte count ratio.

contributes to the simplicity of this score. Instead, it is formed by laboratory values related to a patient's adaptive immune response. In previous reports, the nomenclature of the scoring system differed between studies: an absolute monocyte and lymphocyte prognostic index<sup>[14,18]</sup>, an absolute monocyte/lymphocyte count prognostic score<sup>[15]</sup>, an absolute monocyte and lymphocyte prognostic score<sup>[16]</sup>, and an immunological index<sup>[17]</sup>. All of the scoring systems stratified patients into three risk groups: low risk (both low AMC and high ALC), intermediate risk (either high AMC or low ALC), and high risk (both high AMC and low ALC). In most of the studies, both AMC and ALC were dichotomized into high and low groups by using predefined cut-off points<sup>[14,15,17]</sup> developed by Wilcox *et al.*<sup>[16]</sup> to enable comparison between studies irrespective of optimal cut-off points.

In the study by Wilcox *et al.*<sup>[16]</sup>, the cut-off point for AMC (630/ $\mu$ L) was determined by ROC curve analysis, whereas the cut-off point for ALC (1000/ $\mu$ L) was determined by the fact that it has been utilized in many previous studies on lymphoma<sup>[22-25]</sup>. In some of those studies, the choice of 1000/ $\mu$ L as the cut-off point for ALC was supported by the fact that it yielded the greatest differential in survival<sup>[23,25]</sup>. On the other hand, in a study by Huang *et al.*<sup>[18]</sup>, the cut-off points of both AMC and ALC were determined by ROC curve analysis.

Based on previous reports, we initially evaluated the predefined cut-off point (630/ $\mu$ L for AMC and 1000/ $\mu$ L for ALC) according to the report by Wilcox *et al.*<sup>[16]</sup> in our cohort, but using this value, no patient belonged to the high-risk group. When comparing low- and intermediate-risk groups with the log-rank test, no statistical significance was obtained for factors predicting DFS ( $P = 0.3295$ ) or OS ( $P = 0.1315$ ). In addition, when dichotomizing AMC and ALC by using the predefined value for gastric cancer described by Bruckner *et al.*<sup>[9]</sup> (300 to 900/ $\mu$ L vs others for AMC, and  $< 1500/\mu$ L vs  $\geq 1500/\mu$ L for ALC) and combining them to produce three risk groups of AMLPS, the log-rank test revealed no statistical significance in predicting DFS ( $P = 0.1725$ ) or OS ( $P = 0.0640$ ). In our study, both AMC and ALC were dichotomized into two groups by using cut-off points that were determined by ROC curve analysis for survival (672.4/ $\mu$ L for AMC and 1734/ $\mu$ L for ALC), and an AMLPS with three risk groups were generated, revealing statistical significance for predicting DFS and OS.

In our study, we also intended to analyze the role of host-related factors together, including the serum albumin concentration, platelet count, MPV, NLR, and PLR, to avoid confounding effects. In gastric cancer, serum albumin is reportedly a significant factor for survival<sup>[13]</sup>. The platelet count is a convenient parameter within the blood cell count that can help to predict patients' survival. MPV is a laboratory marker associated with platelet function, and a role for MPV as possible biomarker in the early diagnosis and

monitoring of gastric cancer has been suggested<sup>[8]</sup>. The NLR also reflects inflammatory status. An elevated NLR has been reported to be a convenient biomarker to identify patients with a poor prognosis in primary gastric cancer<sup>[10-12]</sup>. The PLR has been introduced as a prognostic scoring system in various cancers, including gastrointestinal cancer<sup>[20,21]</sup>. In a recent report, PLR was an independent prognostic factor for OS rates in patients with advanced gastric cancer treated with chemotherapy<sup>[12]</sup>. In our study, the relationship between DFS and the serum albumin concentration, platelet count, MPV, NLR, or PLR showed statistical significance in univariate analysis, but none reached statistical significance in multivariate analysis. In addition, the relationship between OS and the various inflammatory markers mentioned above also showed statistical significance in univariate analysis, but they also did not reach statistical significance in multivariate analysis. Therefore, the AMLPS was independent of previously evaluated inflammatory markers.

Though the detailed mechanism still remains unclear, monocytes are known to promote tumorigenesis and angiogenesis<sup>[26]</sup> and suppress the host immune response to cancer, which may explain why elevated monocyte counts in solid tumors confer a negative prognosis<sup>[27]</sup>. Monocytes in the circulation are an important source of soluble mediators, which may help support the evolution of malignant cells<sup>[16,28]</sup>. Lymphocytes are markers of host immune competence<sup>[29]</sup>, and they also act as mediators of antibody-dependent cell-mediated cytotoxicity<sup>[30]</sup>; as a result, lymphopenia may be an adverse prognostic feature for gastric cancer. In our study, higher percentages of cases for T3-4, N1-3, and stage III were observed from low-risk to high-risk. In similar fashion a decreased percentages for T1-2, N0, and stage I - II were observed from low-risk to high-risk, supporting the balance between immune surveillance (ALC) versus tumor growth (AMC).

The results of this study should be interpreted cautiously, as they have several limitations. It was a retrospective study with a relatively small sample size and a relatively short median follow-up period. As we mentioned before, different investigators have used different cut-off values for the evaluation of ALC and AMC, and their unification for clinical application may require further exploration<sup>[31]</sup>. In addition, the AMC and ALC levels may vary in the same patient from day-to-day, not static<sup>[31]</sup>. To overcome this limitation, we evaluated AMLPS together with well-known predictors like serum albumin concentration, platelet count, MPV, NLR, and PLR<sup>[32]</sup>. In addition, data of CBCs just before the operation was collected to avoid any inflammatory effects of preoperative serial evaluation following diagnosis. Finally, we could not reach a conclusion whether three risk groups can be changed if venous blood is taken for AMC and ALC several times before operation. The reason is that only one preoperative data of CBC was available in most of the patients, and even though several preoperative CBCs were available,

the result may have been affected by preoperative procedures.

In conclusion, the AMC and ALC were combined to generate a prognostic score, the AMLPS, which is a simple tool that could be used as a prognostic model for patients with gastric cancer. This prognostic score was independent of various inflammatory factors, age, and pathologic stage. These results should be validated in prospective trials.

## COMMENTS

### Background

Gastric cancer represents one of the major causes of cancer mortality worldwide. Despite a result of advances in surgical treatment, the role of surgery as mainstay treatment is limited to around a quarter of all patients, and overall survival of patients who undergo surgery progressively diminishes as stage increases, ranging from 75% for stage I to 35% or less for stage II and beyond; accurately predicting patients' prognoses is needed to improve patient survival and to provide important information to the patients.

### Research frontiers

Assessment of the inflammatory response to the tumor may be easier and more-cost effective in clinical practice, and the addition of inflammatory factors to tumor-associated factors would be expected to help in disease management.

### Innovations and breakthroughs

This study aims to measure the prognostic significance of absolute monocyte count/absolute lymphocyte count prognostic score (AMLPS) in patients with gastric cancer. The prognostic value of absolute monocyte count (AMC) in gastric cancer has not been validated ever before.

### Applications

AMC and absolute lymphocyte count were combined to generate a prognostic score, the AMLPS, which is a simple tool that could be used as a prognostic model for patients with gastric cancer. This prognostic score was independent of various inflammatory factors, age, and pathologic stage. These results should be validated in prospective trials.

### Peer-review

The paper is to measure the prognostic significance of absolute monocyte count/AMLPS in patients with gastric cancer and to assess the AMLPS as an independent prognostic factor for survival in comparison with known prognostic factors. Although some published paper have showed the same change in hematological tumor, the finding in solid cancer in this paper should actually be interpreted cautiously.

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P- Reviewer: Porrata LF, Qi F S- Editor: Yu J L- Editor: A  
E- Editor: Wang CH





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ISSN 1007-9327

