Metastatic lymph node ratio in advanced gastric carcinoma: A better prognostic factor than number of metastatic lymph nodes?

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Abstract. Gastric carcinoma is the most common cancer and the second most common cause of cancer-related death in Korea. Many studies have been reported regarding prognostic factors. Among the category I prognostic factors of gastric carcinoma, lymph node metastasis (nodal status) is considered to be the strongest prognostic factor. According to the current UICC (the International Union Against Cancer)/AJCC (American Joint Committee on Cancer) staging system, nodal status is categorized based on the number of metastatic lymph nodes (pN0, no metastasis; pN1, 1-6 lymph nodes positive; pN2, 7-15 and pN3, >15). Some groups have recently proposed the metastatic lymph node ratio (the ratio between metastatic lymph nodes and total dissected lymph nodes; MLR) as an alternative prognostic factor to supplement the limitations of the conventional N staging system, particularly when a limited number of lymph nodes is obtained. In the present study, we aimed to evaluate which lymph node assessment method, metastatic lymph node number vs. ratio of metastasis, was better to predict survival in comparison with known prognostic factors in advanced gastric carcinoma in Korea. In addition, we tried to determine what level of MLR was a statistically significant factor to get a meaningful separation of survival. Based on our study, we demonstrate that the MLR was a simple and reproducible prognostic factor that supplemented the limitation of the conventional N staging system, and provided more accurate prognostic stratification in advanced gastric cancer. In addition to patients' age, tumor size, and chemotherapy, MLR was a strong prognostic factor in multivariate analysis, although the number of lymph node metastases, was not a strong factor. The MLR demonstrated further survival influence in pN2 stage. Moreover, with the relationship to pT stage, MLR showed better survival information than that of ordinary AJCC pN stage. We also propose that the optimal cut off values for the MLR should be classified into four groups as follows: MLR0, 0; MLR1, >0-0.3; MLR2, >0.3-0.6 and MLR3, >0.6.

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Introduction

Gastric carcinoma is one of the most common cancers in many Asian countries including Korea and Japan, and the second most common cause of cancer-related death worldwide. Many studies have been reported regarding the causes, prognostic factors and treatments of gastric carcinoma.

Among the known category I prognostic factors of gastric carcinoma, depth of invasion and lymph node metastasis (nodal status) are considered to be most important. However, there is still controversy regarding the appropriate classification of nodal status, as well as the significance of positive lymph node number vs. metastatic lymph node ratio, and no definite consensus has yet been reached on either issue. However, according to the current UICC (the International Union Against Cancer)/AJCC (American Joint Committee on Cancer) staging system, which is the most widely used, nodal status is categorized based on the number of metastatic lymph nodes (pN0, no metastasis; pN1, 1-6 lymph nodes positive; pN2, 7-15 and pN3, >15) (1,2). This staging system, which is based on the number of metastatic lymph nodes, is a simple and reproducible method. However, when the AJCC/UICC staging system is used, the phenomenon of stage migration has been observed in about 10-15% of cases (8,9,13-15); also, more than 15 lymph nodes should be examined for correct assessment of N staging.

In Japan, the status of lymph node metastasis is classified according to the anatomical location by the Japanese Classification of Gastric Carcinoma (JCGC) (3). To acquire sufficient knowledge on the lymph node status, extended lymph node dissection (D2 or D3) should be performed. With a limited lymph node dissection (D1 dissection), with only perigastric lymph node assessment, a complete nodal staging cannot be

obtained. In some Western countries where only D1 dissection is performed, the JCGC N staging systems cannot be applied to routine practice.

Some studies have recently proposed the MLR (the ratio between the number of metastatic lymph nodes and the number of total dissected lymph nodes; MLR) as an alternative prognostic factor to supplement the limitations of conventional N staging system (4-12), particularly when a limited number of lymph nodes is obtained. In the present study, we aimed to evaluate which lymph node assessment method, metastatic lymph node number vs. ratio of metastasis, was better to predict the survival in comparison with known prognostic factors in advanced gastric carcinoma in Korea. In addition, we tried to determine what level of MLR was statistically a significant factor to get a meaningful separation of survival.

Materials and methods

Patient selection. This retrospective study examined 495 patients who were diagnosed as advanced gastric adenocarcinoma at Asan Medical Center, Seoul, Korea in 2002. The eligibility criteria were as follows: a) Patients underwent radical gastrectomy (distal gastrectomy, total gastrectomy, or extended gastrectomy) at Asan Medical Center in the year 2002, b) cases with more than 15 lymph nodes were dissected and pathologically examined, and c) patients had at least 2 years of follow-up. Patients with distant metastasis (e.g. liver, lung, peritoneal dissemination) or serious concomitant disease at the time of diagnosis were excluded. Based on the above criteria, a total number of 342 gastric cancer patients were included in the study.

Clinicopathological analysis. Demographic data with patients' age, sex, type of surgery and adjuvant chemotherapy as well as pathologic findings including tumor size, location, depth of tumor invasion, presence of lymphovascular invasion, Lauren's classification and tumor grading were reviewed.

Classifications of lymph node status. The pN categories were divided into pN0 (no lymph node metastasis), pN1 (1-6 metastatic lymph nodes), pN2 (7-15 metastatic lymph nodes), and pN3 (more than 15 metastatic lymph nodes) according to the 6th edition of AJCC staging manual (2). The lymph node location was classified as Group 1 (perigastric lymph nodes), Group 2 (lymph nodes around the left gastric artery, splenic artery, common hepatic artery, and celiac axis), and Group 3 (lymph nodes around the root of mesentery, hepatoduodenal ligament, and posterior aspect of pancreas) based on JCGC (3). The MLR was calculated as the ratio between the number of metastatic lymph nodes and total dissected lymph nodes. The MLR intervals were determined by the best cut off approach considering the patients' disease-free survival as the dependent variable. The cut off values that we found were as follows: MLR0, 0; MLR1, >0-0.3; MLR2, >0.3-0.6 and MLR3, >0.6.

Statistical analysis. The survival analysis was calculated according to the Kaplan-Meier method and compared by log-rank test. Both the disease-free survival and overall survival

Table I. Clinicopathological characteristics of the patients.

Factors	Number (%)
Sex	
Male	236 (69.01)
Female	106 (30.99)
Age	
<65	171 (50.00)
≥65	171 (50.00)
Tumor size	
<5 cm	121 (35.38)
5-10 cm	186 (54.38)
≥10 cm	35 (10.24)
Tumor location	
Upper third	65 (19.01)
Middle third	86 (25.15)
Lower third	136 (39.77)
Diffuse	55 (16.08)
T category	
T2a	70 (20.47)
T2b	137 (40.06)
T3	121 (35.38)
T4	14 (4.09)
Lymphovascular invasion	
Yes	149 (43.57)
No	193 (56.43)
Lauren's classification	
Intestinal	201 (58.77)
Diffuse	97 (28.36)
Mixed	44 (12.87)
N stage	
N0	90 (26.32)
N1	148 (43.27)
N2	78 (22.81)
N3	26 (7.60)
Metastatic lymph node ratio	
N ratio 0	90 (26.32)
N ratio 1	168 (49.12)
N ratio 2	60 (17.54)
N ratio 3	24 (7.60)
Chemotherapy	
Yes	251 (73.59)
No	91 (26.61)
Lymph node location	
No metastasis	90 (26.32)
Group 1	174 (50.88)
Group 2	68 (19.88)
Group 3	10 (2.92)
Surgery	
Distal gastrectomy	214 (62.57)
Total gastrectomy	110 (32.16)
Extended radical gastrectomy	18 (5.26)
Histologic grade	
G1 (Well differentiated)	18 (5.26)
G2 (Moderately differentiated)	88 (25.73)
G3 (Poorly differentiated)	236 (69.01)

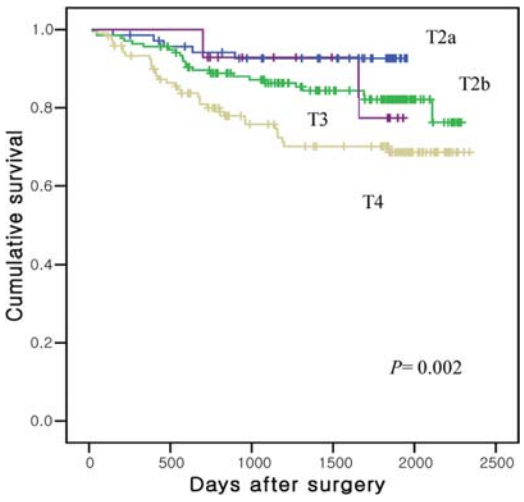


Figure 1. Kaplan-Meier survival curves of patients according to T stage (depth of invasion; pT2a, muscularis propria; pT2b, subserosa; pT3, serosa penetration; pT4, invasion to adjacent structures).

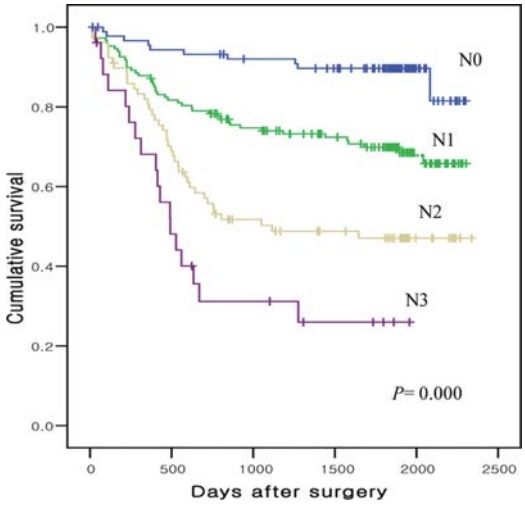


Figure 2. Kaplan-Meier survival curves of patients according to pN stage. (pN0, no metastatic lymph node; pN1, 1-6 metastatic lymph nodes; pN2, 7-15 metastatic lymph nodes; pN3, >15 metastatic lymph nodes).

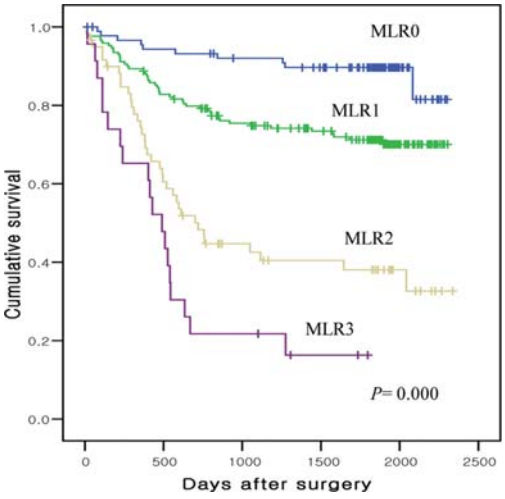


Figure 3. Kaplan-Meier survival curves of patients according to metastatic lymph node ratio (MLR). (MLR0, no metastatic lymph node; MLR1, 0.01-0.30; MLR2, >0.30-0.60; MLR3, >0.60).

were estimated. The time of survival was estimated from the date of diagnosis to death. To evaluate whether the MLR was a better prognostic factor compared to the conventional N staging system, these two nodal assessments, number vs. ratio, were compared with the depth of tumor invasion and overall survival. Moreover, MLR was stratified in the same pT and pN categories, to assess if MLR showed any survival benefit where the conventional staging system failed to predict any benefit. On this additional analysis, pT categories were divided into two groups; a) pT2 as one group, b) pT3 and 4 together as another group. Univariate and multivariate analyses of prognostic factors were performed using the Cox proportional hazard model and selected in step-wise procedure with backward elimination. Survival rates were taken in their 95% confidence intervals. The accepted level of significance was $p<0.05$. The data were analyzed with SPSS 12.0 statistics for Windows statistical software (SPSS Inc., Chicago, IL).

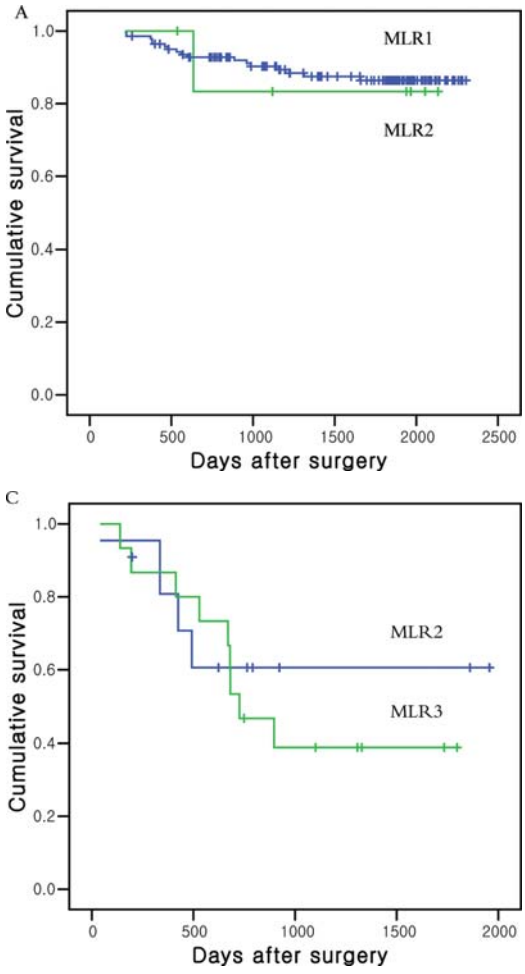
Results

Of the total 342 patients, 236 patients were men, and 106 were women, and the median age of the patients was 62 years ranging from 29 to 88 years. The median follow-up period of time was 53.4 months. Total number of dissected lymph nodes ranged from 16 to 98, with a median number of 28.9. According to the UICC/AJCC system (based on the number of metastatic lymph nodes), 90 (26.32%) patients had no metastasis, 148 (43.27%) belonged to pN1, 78 (22.81%) to pN2, and 26 (7.60%) were classified as pN3. The distribution of lymph nodes by anatomic location is as follows: 174 (50.88%) for Group 1, 68 (19.88%) for Group 2, and 10 (2.92%) for Group 3. The size of primary tumors ranged from 0.6 to 21 cm with a mean of 6.18 cm. There were 70 cases in pT2a, 137 in pT2b, 121 in pT3, and 14 in pT4. More details of the patient characteristics are listed in Table I.

The survival curves according to depth of invasion (T stage), number of metastatic lymph nodes (N stage), and MLR are shown in Figs. 1-3. The N stage and MLR both correlated well with the prognosis of the gastric cancer patients (p=0.000). However, the T stage did not have as much statistical significance as did the AJCC N stage and MLR.

Kaplan-Meier survival curves of MLR stratified by pT stage and pN stage are seen in Fig. 4A-C and Fig. 5A and B. MLR demonstrated a statistically significant difference in survival in both the pT2 and the pT3/pT4 groups (Fig. 5A and B). In cases of pN2 category, the MLR independently revealed statistically significant survival difference (Fig. 4B). However, there were no statistically significant survival differences in pN1 or pN3 categories (Fig. 4A and C). Similarly, pN stage was stratified by MLR, to assess if pN stage predicted survival difference in the same MLR stage (Fig. 6A-C). As the result of the analysis, pN stage failed to predict any survival difference in any category of MLR.

Among the many variable factors of gastric cancer patients, the univariate analysis showed that age, pT stage (depth of invasion), pN stage (number of metastatic lymph nodes),



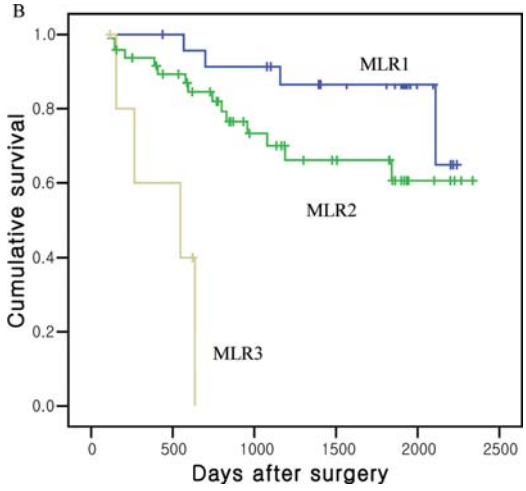


Figure 4. (A) Kaplan-Meier survival curves of pN1 stratified by MLR. No MLR3 in this group. (B) Kaplan-Meier survival curves of pN2 stratified by MLR. (C) Kaplan-Meier survival curves of pN3 stratified by MLR. No MLR1 in this group.

MLR, tumor size, type of surgery, Lauren's classification, and location of metastatic lymph nodes [by Japanese Classification of Gastric Carcinoma (JCGC)], lymphovascular invasion, and chemotherapy were statistically significant prognostic factors (Table II).

On multivariate analysis, following the backward elimination, MLR, age, tumor size, and chemotherapy were shown as independent prognostic factors. Among them, the MLR was the most significant factor (Table III). Nodal status (pN) was not an independent prognostic factor on multivariate analysis.

Discussion

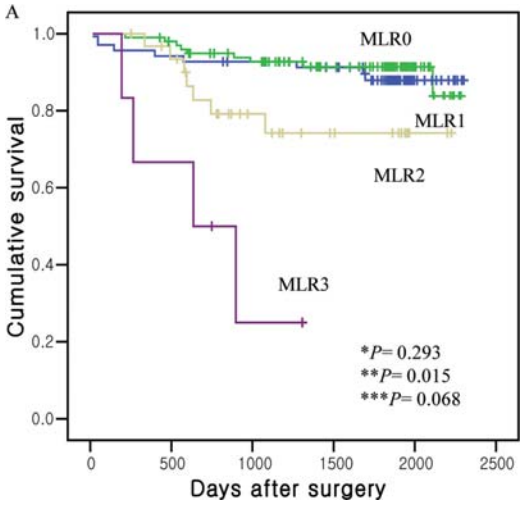
Gastric carcinoma is one of the most common cancers as well as one of the most common causes of cancer death worldwide and the category I prognostic factors include stage and grade. At present, the two main staging systems of gastric carcinoma are AJCC/UICC and JCGC. Among the variable factors that could effect the survival of gastric carcinoma patients, lymph node status is known to be one of the most powerful prognostic factors.

However, AJCC/UICC and JCGC evaluate the metastatic lymph node status in different ways. AJCC/UICC system classifies the nodal status according to the number of metastatic lymph nodes as pN0, no lymph node metastasis; pN1, 1-6 lymph nodes metastasis; pN2, 7-15 and pN3, >15 (1,2). In the JCGC system, on the other hand, the anatomical location of metastatic lymph nodes is used as a key parameter (3). Although both AJCC/UICC and JCGC systems provide useful information on predicting the survival of gastric cancer patients, there have been some limitations.

When the AJCC/UICC staging system is used, the phenomenon of stage migration has been observed in about 10-15% of cases (8,9,13-15), and at least 15 lymph nodes (and ideally more than 15 lymph nodes) should be examined for the correct assessment of nodal pN status. Similarly, as for the JCGC system, to acquire sufficient knowledge on the lymph node status, extended lymph node dissection (D2 or D3) should be performed; with a limited lymph node dissection (D1 dissection) that has been the standard treatment in the Western countries, no detailed nodal information can be obtained other than the status of perigastric (D1) lymph nodes.

Recently, to supplement the limitations of conventional pN staging system, some previous studies have proposed the metastatic lymph node ratio (the ratio between metastatic lymph nodes and total dissected lymph nodes; MLR) as an alternative prognostic factor (4-12). In accordance with the published findings of the previous groups, the present study proved that MLR was better than the current pN staging system and showed a strong correlation with pT stage (depth of invasion) (Figs. 2, 3 and 5).

In pN2 stage, MLR demonstrated a further separation of patient survival (Fig. 4B). However, in pN1 or pN3, there was no additional impact (Fig. 4A and C). The conventional clinicopathological parameters including the patient age, pT stage (depth of invasion), pN stage (number of metastatic lymph nodes), tumor size, type of surgery, Lauren's classification, and location of metastatic lymph nodes (by JCGC), lymphovascular invasion and chemotherapy as well as MLR were important to predict patient survival in univariate analysis. Moreover, the present study demonstrated that MLR was a strong prognostic factor on both univariate and multivariate analysis besides the patient age, tumor size and chemo-



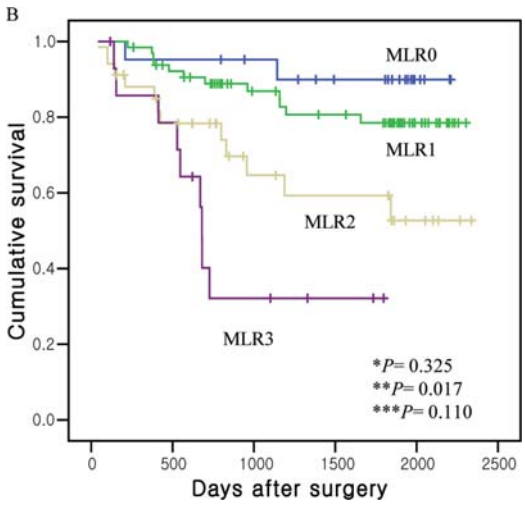
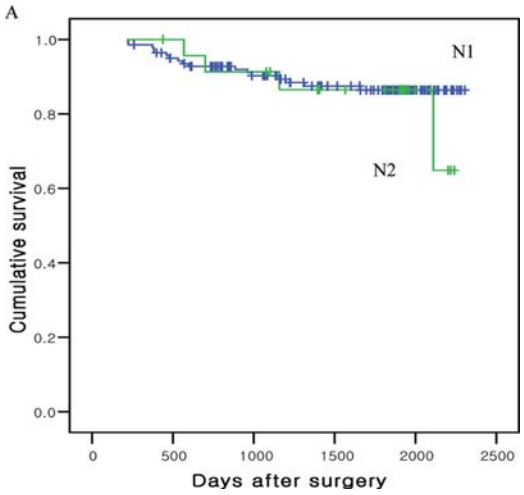
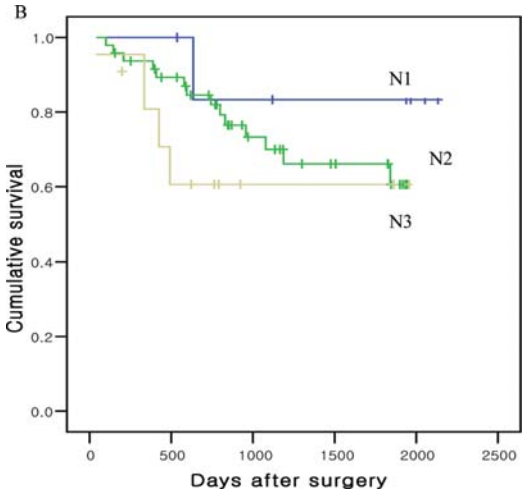


Figure 5. (A) Kaplan-Meier survival curves of pT2 stratified by metastatic lymph node ratio (MLR). (B) Kaplan-Meier survival curves of pT3 and pT4 stratified by metastatic lymph node ratio (MLR). (*p, the p-value between MLR0 and MLR1; **p, between MLR1 and MLR2; and ***p, between MLR2 and MLR3).





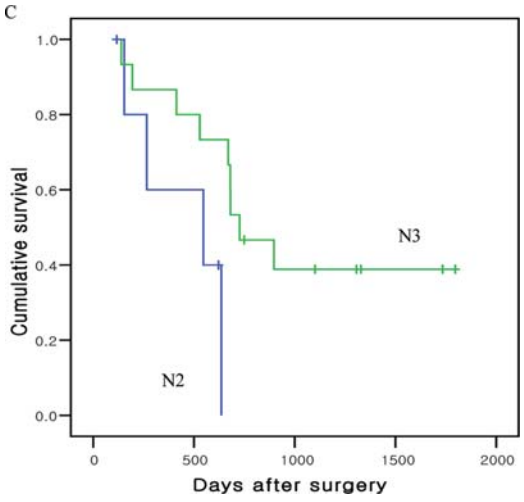


Figure 6. (A) Kaplan-Meier survival curves of MLR1 stratified by pN stage. (B) Kaplan-Meier survival curves of MLR2 stratified by pN stage. (C) Kaplan-Meier survival curves of MLR3 stratified by pN stage.

therapy (Table II and III). Other factors, including pN stage, proved not to be important predictors in multivariate analysis.

The present study, as well as some other studies, proved that MLR was a better prognostic factor than the conventional pN staging system, however, no consensus has been made on the optimal categorization of MLR, for each study was carried out by different standardization. For reasonable classification, we categorized the patients into ten subgroups on the basis of 0.1 intervals of MLR, and then reclassified into four groups by analyzing the survival rate to find out the best cut off values. Based on our data, the optimal cut off values appeared MLR0, 0; MLR1, 0-0.3; MLR2, >0.3-0.6 and MLR3, >0.6. Similar to the present result, a previous study in China by Yu and Li (16), mainly focusing on setting up a standard staging of MLR, also claimed that the best cut off values of MLR turned out to be the same as our study (MLR0, 0; MLR1, >0-0.3; MLR2, >0.3-0.6 and MLR3, >0.6) (16).

In conclusion, the MLR is a simple and reproducible prognostic factor that supplements the limitation of the conventional N staging system, and provides more accurate prognostic stratification in advanced gastric cancer. Based on the results above, we propose replacing pN staging system with MLR to provide both the patients and clinicians more evidence-based and accurate prognostic information.

Table II. Univariate analysis of various prognostic factors.

Factors	Hazard ratio	95% Confidence interval	P-value
Age	1.019	1.002-1.037	0.032
Sex	1.059	0.713-1.573	0.777
T stage	1.000		
T2b/T2a	1.818	0.976-3.387	0.060
T3/T2a	2.836	1.544-5.211	0.001
T4/T2a	2.972	1.129-7.827	0.027
N stage	1.000		
N1/N0	3.063	1.543-6.079	0.001
N2/N0	6.170	3.081-12.358	0.000
N3/N0	11.257	5.170-24.510	0.000
MLR	1.000		
MLR1/MLR0	2.853	1.443-5.639	0.003
MLR2/MLR0	8.154	4.036-16.475	0.000
MLR3/MLR0	13.287	6.144-28.735	0.000
Location	1.000		
Middle/Upper	1.235	0.648-2.355	0.521
Lower/Upper	1.567	0.875-2.807	0.131
Diffuse/Upper	3.060	1.633-5.733	0.000
Surgery	1.000		
TG/DG	1.225	0.821-1.829	0.320
ERG/DG	2.474	1.269-4.823	0.008
Grade	1.000		
G2/G1	0.824	0.337-2.017	0.672
G3/G1	1.068	0.564-1.979	0.876
Lauren's classification	1.000		
Mixed/Intestinal	1.056	0.564-1.979	0.865
Diffuse/Intestinal	2.376	1.607-3.513	0.000
Chemotherapy	0.245	0.132-0.457	0.000
Lymphovascular invasion	0.557	0.384-0.807	0.002
Lymph node location	1.000		
Group 1/Group 0	3.577	1.887-6.779	0.000
Group 2/Group 0	4.998	2.501-9.988	0.000
Group 3/Group 0	8.059	3.115-20.848	0.000
Tumor size	1.123	1.073-1.174	0.000

MLR, metastatic lymph node ratio; TG, total gastrectomy; DG, distal gastrectomy; ERG, extended radical gastrectomy.

Table III. Multivariate analysis of various clinicopathological factors.

Factors	Hazard ratio	95% Confidence interval	P-value
MLR	1.000		0.000
MLR1/MLR0	1.786	0.858-3.718	0.121
MLR2/MLR0	4.607	2.148-9.881	0.000
MLR3/MLR0	7.319	3.154-16.981	0.000
Age	1.028	1.010-1.047	0.002
Tumor size	1.072	1.022-1.125	0.005
Chemotherapy	0.380	0.189-0.763	0.007

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