**Original Article**

# The value of preoperative lymphocytes-to-monocytes ratio in predicting lymph node metastasis in gastric cancer

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**Background:** This study was aimed to evaluate value of preoperative lymphocytes-to-monocytes ratio (LMR) as a predictor for lymph node metastasis in gastric cancer.

**Methods:** Patients with pathologically diagnosed malignant gastric tumor were reviewed retrospectively. Patients' demographic data, clinical manifestations and LMR were collected. The postoperative pathology data including the tumor size, tumor sites, differentiation degree of tumor, depth of tumor invasion, metastatic lymph nodes, total dissected lymph nodes, distant metastasis, vessel carcinoma embolus, neural invasion, Lauren's classification, Ki-67 and TNM stage were collected. Receiver operating characteristic curve (ROC) was used to determine the cut-off point of LMR. The association between LMR and the clinicopathologic factors was further analyzed.

**Results:** A total of 177 subjects were enrolled into the study. LMR =3.79 was used as cut-off point; the patients with LMR ≥3.79 were classified as high-LMR group (123 cases) and the patients with LMR <3.79 as low-LMR group (54 cases). LMR was an independent risk factor for lymph node metastasis.

**Conclusions:** Low preoperative LMR was positively correlated with lymph node metastasis in gastric cancer patients, and had predictive value for lymph node metastasis in gastric cancer patients.

**Keywords:** Gastric cancer; lymphocyte-to-monocyte ratio (LMR); lymph node metastasis

## Introduction

Stomach cancer is the fifth most-common cancer in the world and the number of stomach cancer-resulted death was 700,000 in 2012, making it the third-leading cause of cancer-related death (1). In many countries and regions, due to lack of screening, the 5-year survival rate of gastric cancer was only 20% and was 10–15% in advanced gastric cancer (2,3). Lymph node metastasis is associated with the prognosis of gastric cancer and has been acknowledged as an independent indicator of poor prognosis (4,5). There

is no obvious symptoms in the early stage, however, lymph node metastasis usually has occurred when stomach cancer is diagnosed. Therefore, it is critical to make an early and accurate prediction of lymph node metastasis for the diagnosis of gastric cancer, staging, treatment and prognosis.

At present, tumor node metastasis (TNM) is widely used for gastric cancer staging. However, the lymph node involvement can only be determined pathologically after surgery. The magnetic resonance imaging (MRI) and computed tomography (CT), endoscopic ultrasound (EUS)

and positron emission tomography computed tomography (PET-CT) were commonly used for preoperative evaluation of lymph node metastasis. But those methods still have disadvantages in accuracy and consistency (6,7). As reported, some protein markers have potential to indicate the lymph node metastasis of gastric cancer (8,9), but those biomarkers are under laboratory research. Therefore, it is critical to find effective methods for assessing lymph node metastasis before surgery.

It is well known that inflammatory reactions play an important role in the process of tumor development, progression, invasion and metastatic prognosis (10). Systemic inflammatory response can inhibit normal apoptosis of senile cells and promote tumor progression, metastasis and diffusion by secreting inflammation factors and cytokines (11). LMR was reported to have the potential to reflect the degree of systemic inflammatory response and be related to the prognosis of gastric cancer (12,13). As far as we know, there are few studies concerning the correlation between LMR and lymph node metastasis of gastric cancer. Therefore, we conducted this study to explore the association between LMR and the clinicopathologic factors, and to determine if LMR is a preoperative predictor for lymph node metastasis in patients with gastric cancer.

## Methods

### Study subjects

The patients with malignant gastric tumor, who received treatment in the department of general surgery, Beijing Shijitan Hospital of Capital Medical University from January 2014 to May 2017, were retrospectively reviewed. The inclusion criteria were patients with pathologically-diagnosed malignant gastric tumor, patients who received surgical treatment and lymph node dissection, and patients without obvious infection, hemorrhage or other hematological disease. The exclusion criteria were patients who had received radiotherapy, chemotherapy, immunosuppressive therapy or other anti-tumor therapy, number of dissected lymph nodes <15, and multiple primary malignant neoplasm. This study was approved by the ethic committee of Beijing Shijitan Hospital of Capital Medical University.

### Data collection

Patients' demographic data were collected. Peripheral venous blood samples were collected and the indexes including lymphocytes, monocytes, CA19-9 and CEA were detected within one week preoperatively. The postoperative pathology was independently analyzed by two experienced pathologists according to Japanese gastric cancer guidelines (14). The following data were collected, including tumor size, tumor sites, differentiation degree of tumor, depth of tumor invasion, metastatic lymph nodes, total dissected lymph nodes, distant metastasis, vessel carcinoma embolus, neural invasion, Lauren's classification, Ki-67 and TNM stage. LMR, percentage of lymph node metastasis and degree of lymphatic metastasis were calculated. Highly differentiated cancers included papillary adenocarcinoma and tubular adenocarcinoma, while highly undifferentiated cancers included signet ring cell carcinoma, mucinous adenocarcinoma and undifferentiated carcinoma. Patients with multiple pathological types of gastric cancer were subject to the least differentiated components. In the patients with multiple pathological types, the least differentiated components were used for analysis.

### Definition

LMR was defined as lymphocyte to monocyte ratio. Percentage of lymph node metastasis was defined as percentage of the patients with metastasis in the whole cohort. Degree of lymphatic metastasis was defined as percentage of the metastatic lymph nodes in all the dissected lymph nodes.

### Statistical analysis

The data were analyzed by SPSS version 20.0 (SPSS Inc, Chicago, IL, USA). Data were presented as mean ± SD for continuous variables or as counts and percentages for categorical variables. Receiver operating characteristic curve (ROC) was used to determine the cut-off point of LMR. The continuous variables were analyzed with independent $t$-test. Fisher test and $\chi^2$ test were used to analyze categorical variables. For non-parametric variables, Mann-Whitney U test were applied. The variables with significant difference between the two groups were decided by univariate logistic regression. Multivariate logistic regression analysis was performed to determine the correlation between LMR and lymph node metastasis. The odds ratio (OR) with 95% confidence interval (95% CI) were obtained. All statistical tests were two-sided. P<0.05 was considered as significant difference.
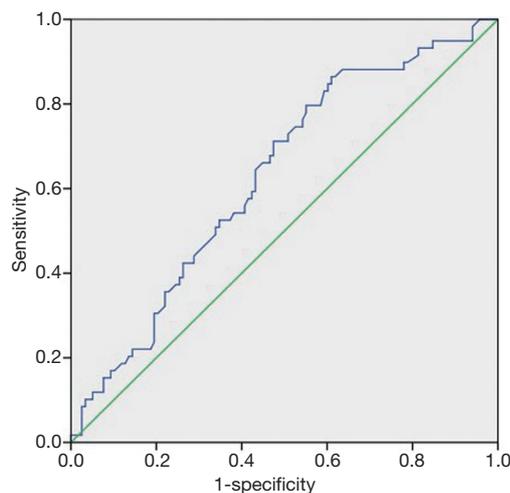
**Figure 1** The receiver operating characteristics (ROC) curve.

## Results

### Baseline data and LMR of the patients

A total of 177 subjects (136 males and 41 females; average age of 60.7±11.7 years old) met the inclusion criteria and were included in the study. Among them, 117 patients (117/177, 66.10%) had lymph node metastasis.

LMR was used to evaluate the possibility of lymph node metastasis; the area under the curve (AUC) of ROC was 0.629 (*Figure 1*). The Youden index was maximum with LMR =3.79. LMR =3.79 was used as cut-off point; the patients with LMR ≥3.79 were classified as high-LMR group (123 cases) and the patients with LMR <3.79 as low-LMR group (54 cases).

In the high-LMR group, there were 70 cases with lymph node metastasis; percentage of lymph node metastasis was 56.9% (70/123). There were 441 positive nodes among 3,749 dissected lymph nodes; degree of lymphatic metastasis was 11.8% (441/3,749). In the low-LMR group, there were 47 cases with lymph node metastasis; percentage of lymph node metastasis was 87.0% (47/54). There were 534 positive nodes among the 1,548 dissected lymph nodes; degree of lymphatic metastasis was 34.5% (534/1,548). The percentage of lymph node metastasis and the degree of lymphatic metastasis were significantly lower in the high-LMR group than those in the low-LMR group.

### Comparison of clinicopathological characteristics between the high-LMR group and the low-LMR group

The statistical results showed that there' no significant

difference (P>0.05) in sex, age, tumor diameter, degree of differentiation, neural invasion, preoperative carcino-embryonic antigen (CEA), carbohydrate antigen-19-9 (CA19-9) and Ki-67 (*Table 1*) between those two groups. There's significant difference (P<0.05) in the tumor site, infiltration depth, lymph node metastasis, number of metastatic lymph nodes >6, TNM stage, blood vessel invasion and Lauren's types between high-LMR group and low-LMR group.

### Multiple logistic regression analysis for lymph node metastasis

The factors with significant difference between high-LMR group and low-LMR group were used for multiple logistic regression analysis. LMR was an independent risk factor for lymph node metastasis. The OR value was listed in *Table 2*.

## Discussion

LMR has been gaining more and more attention as an indicator of inflammatory response with several studies having found that LMR played a protective role in the prognosis of gastric cancer (12,15). In this study, we mainly found that low LMR was positively correlated with lymph node metastasis and lymph node metastasis stage in gastric cancer patient; LMR might have the potential as a preoperative predictor for lymph node metastasis in gastric cancer.

Lymphocyte plays a role in inhibiting tumor occurrence, development, proliferation and distant metastasis (16,17). As reported, tumor infiltrating lymphocyte was highly related with tumor invasion and metastasis (18,19). The statistical results showed that there's significant difference (P<0.05) in the tumor site, infiltration depth, lymph node metastasis, number of metastatic lymph nodes >6, TNM stage, carcinoma cell embolus and Lauren's types. There's no significant difference (P>0.05) in sex, age, tumor diameter, degree of differentiation, neural invasion, preoperative carcino-embryonic antigen (CEA), carbohydrate antigen-19-9 (CA19-9) and Ki-67. This was in accordance to the previous report (12). It might be attributed to that lower level of lymphocytes may lead to reduced immunological surveillance, and it further decreases lymphocyte mediated anticancer effect (20).

Liu *et al*. (21) reported that more infiltration of lymphocytes around tumor tissues may bring better prognosis, which depended on the anti-tumor activity of lymphocytes. Further study (22) indicated that cytotoxic

**Table 1** Comparison of clinicopathologic variables between high-LMR group and low-LMR group

| Variable | N | LMR (cases) ≥3.79 (N=123) | LMR (cases) <3.79 (N=54) | $\chi^2$ | P value |
|---|---|---|---|---|---|
| Sex | | | | 0.333 | 0.564 |
| Male | 136 | 96 | 40 | | |
| Female | 41 | 27 | 14 | | |
| Age | | | | 3.366 | 0.067 |
| <60 years | 80 | 50 | 30 | | |
| ≥60 years | 97 | 73 | 24 | | |
| Tumor diameter | | | | 3.836 | 0.005 |
| <5 cm | 95 | 72 | 23 | | |
| ≥5 cm | 82 | 51 | 31 | | |
| Tumor site | | | | 26.601 | <0.001 |
| Preventriculus | 53 | 39 | 14 | | |
| Gastric body | 50 | 13 | 37 | | |
| Gastric antrum | 74 | 47 | 27 | | |
| Differentiation degree | | | | 0.838 | 0.360 |
| High or middle | 44 | 33 | 11 | | |
| Low | 133 | 90 | 43 | | |
| Infiltration depth | | | | 11.992 | 0.001 |
| T1/T2 | 59 | 51 | 8 | | |
| T3/T4 | 118 | 72 | 46 | | |
| N-staging | | | | 35.423 | <0.001 |
| N0 | 60 | 53 | 7 | | |
| N1 | 24 | 18 | 6 | | |
| N2 | 41 | 32 | 9 | | |
| N3 | 52 | 20 | 32 | | |
| TNM | | | | 23.409 | <0.001 |
| I | 42 | 38 | 4 | | |
| II | 35 | 30 | 5 | | |
| III | 89 | 48 | 41 | | |
| IV | 11 | 7 | 4 | | |
| Blood vessel invasion | | | | 5.168 | 0.023 |
| + | 102 | 64 | 38 | | |
| − | 75 | 59 | 16 | | |

Table 1 (*continued*)

**Table 1** (*continued*)

| Variable | N | LMR (cases) ≥3.79 (N=123) | LMR (cases) <3.79 (N=54) | $\chi^2$ | P value |
|---|---|---|---|---|---|
| Neural invasion | | | | 0.619 | 0.432 |
| + | 107 | 72 | 35 | | |
| − | 70 | 51 | 19 | | |
| CEA | | | | 0.068 | 0.795 |
| ≤5 | 143 | 100 | 43 | | |
| >5 | 34 | 23 | 11 | | |
| CA199 | | | | 0.082 | 0.774 |
| <37 | 146 | 102 | 43 | | |
| ≥37 | 31 | 21 | 10 | | |
| Lauren's type | | | | 9.551 | 0.008 |
| Intestinal type | 68 | 55 | 13 | | |
| Mixed | 42 | 24 | 18 | | |
| Diffused | 67 | 54 | 13 | | |
| Ki-67 | | | | 0.757 | 0.685 |
| <25% | 12 | 7 | 5 | | |
| 25–50% | 44 | 31 | 13 | | |
| >50% | 121 | 85 | 36 | | |
| Lymph node metastasis | | | | 15.20 | <0.001 |
| No | 60 | 53 | 7 | | |
| Yes | 117 | 70 | 47 | | |
| Number of metastatic lymph nodes | | | | 33.441 | <0.001 |
| ≤6 | 125 | 103 | 22 | | |
| >6 | 52 | 20 | 32 | | |

LMR, lymphocyte to monocyte ratio.

T cells and tumor infiltrated T cells were correlated with lymph node metastasis and survival of gastric cancer. The percentage of lymph node metastasis and the degree of lymphatic metastasis were significantly lower in the high-LMR group than those in the low-LMR group. As for N-stage, the percentage of low LMR was significantly higher in N3 group than in N1 group and N2 group. It suggested that low-LMR might mean higher the percentage of lymph node metastasis, the degree of lymphatic metastasis and lymph node stage. The layers of

**Table 2** Odds ratio for lymph node metastasis according to multivariate logistic regression analysis

| Variable | OR (95% CI) | P value |
|---|---|---|
| Age (≥60 years) | 0.915 (0.417–2.009) | 0.825 |
| Tumor diameter (≥5 cm) | 2.522 (1.023–6.219) | 0.044 |
| Tumor site | | |
| Gastric body | 0.465 (0.161–1.338) | 0.156 |
| Gastric antrum | 0.521 (0.192–1.414) | 0.200 |
| T stage (T3/T4) | 2.017 (0.803–5.069) | 0.136 |
| Blood vessel invasion | 0.339 (0.157–0.729) | 0.006 |
| Lauren's type | | |
| Mixed | 1.164 (0.432–3.132) | 0.764 |
| Diffused | 3.350 (1.307–8.587) | 0.012 |
| LMR | 0.229 (0.081–0.650) | 0.006 |

LMR, lymphocyte to monocyte ratio; OR, odds ratio.

the gastric wall, especially the submucosa and subserosa, are rich in lymphatic duct network, which are favorable for lymphatic metastasis in patients with gastric cancer (23). The decrease of LMR suggests that there's less lymphocyte infiltration in the cancer tissue area, which creates a favorable condition for cancer cells metastasizing to lymph nodes. With the decrease of lymphocyte cells, lymph node metastasis increases, which is in accordance to the "immunological monitoring" theory of B lymphocytes (24). Most studies have shown that increased density of tumor-associated macrophages (TAMs) in tissues can lead to poor prognosis (25). In this study, logistic regression analysis suggested that LMR was an independent predictor of lymph node metastasis.

## Conclusions

There are some limitations in this study, such as small sample size and the nature of retrospective study. In conclusion, low preoperative LMR was positively correlated with lymph node metastasis in gastric cancer patients, and had predictive value for lymph node metastasis in gastric cancer patients. Further study is needed to validate this conclusion.

## Acknowledgments

## Footnote

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