

# Prognostic Significance of Metastatic Lymph Node Ratio in Patients with Gastric Cancer: an Evaluation in North-East of Iran

Ali Taghizadeh-Kermani<sup>1,2</sup>, Seyede Zeinab Yahouiyani<sup>3</sup>, Mohsen AliAkbarian<sup>2</sup>, Mehdi Seilanian Toussi<sup>1</sup>

## Abstract

**Background:** In this study we have evaluated the prognostic impact of Metastatic Lymph node Ratio (MLR) in gastric cancer patients whose have undergone curative surgical resection.

**Methods:** A total of 121 patients with gastric adenocarcinoma undergoing curative surgical resection (R0) in our institutions between 2003 and 2010 have been included in this study. MLR has classified into 3 groups as follows: MLR0; 0, MLR1; >0-0.33 and MLR2; 0.34-1. We have used Kaplan-Meier method to calculate survival rates and log rank test to compare survival curves between groups. Cox proportional hazards model has utilized for multivariate analysis.

**Results:** The median age of patients was 65 (range; 32 to 89) with a male to female ratio of 91/30 (3.03). 88 patients have undergone total gastrectomy (72.5%) and 33 subtotal gastrectomy (27.5%). With a median total retrieved lymph node of 11 (range; 6 to 44), the MLR0 to MLR2 has calculated in 28(23.1%), 31(25.6%) and 62 (51.2%) patients respectively. MLR2 (>0.33) has significantly associated with higher Tumor stage (T1-T2: 18.7% vs. T3: 56.2%,  $p=0.002$ ). With a median follow up time of 12 months (range; 2-88), the 3-year survival in patients with MLR0, MLR1 and MLR2 was 75.1%, 54.8% and 9.5% respectively ( $p$  value<0.001). Tumor location ( $p<0.01$ ), tumor stage ( $p<0.01$ ) and lymph node stage ( $p<0.001$ ) were also significant predictor of survival. MLR has also significant correlated with survival in 91 patients with less than 15 obtained lymph nodes ( $p<0.001$ ). Cox-regression multivariate analysis has shown MLR as the most important and independent predictor of survival ( $p<0.001$ ).

**Conclusion:** MLR with cutoff point of 0.33 could be used as an independent prognostic factor in gastric cancer patients whose have undergone curative surgical resection. This factor could effectively predict survival even in cases with insufficient (<15) retrieved lymph nodes.

**Keywords:** Gastric cancer; Lymph node; Prognosis; Metastatic lymph node ratio

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## Introduction

Gastric cancer is one of the most common cancers in the world, which has known as the second leading cause of cancer deaths worldwide. Every year, more than 930,000 new cases of gastric cancer have diagnosed worldwide which has followed by 700,000 deaths.

Gastric cancer was diagnosed in advanced stages in most cases. The only potentially curative treatment is complete surgical resection. Approximately, 70-80% of patients have regional lymph node involvement. Lymph node status as the extent of involved lymph nodes has been shown as the most important pathological prognostic factors

1. Cancer Research Center, Omid Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

2. Surgical Oncology Research Center, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

3. Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

### Corresponding Author:

Mohsen Aliakbarian, MD;

Assistant professor of Surgery

Tel: (+98) 511 802 2677

Email: Aliakbarianm@mums.ac.ir

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affecting survival in patients whose undergone curative surgery [1].

In both staging systems of American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC), lymph node staging have based on the number of positive lymph nodes. In these systems, retrieval of at least 15 lymph nodes has recommended to acquire correct lymph node status. In Japanese Classification of Gastric Cancer (JCGC) system which the anatomical location of positive lymph nodes matters, extensive dissection of lymph nodes (D2/D3) has proposed in order to gain enough knowledge about lymph node status [2].

The ratio of metastatic lymph nodes to total removed lymph nodes (MLR) is a proposed method that could replace the current lymph node staging systems. Recently, several studies have shown the prognostic effect of MLR in patients with gastric cancer [3-4].

In this study, we have evaluated some potential clinical and pathological prognostic factors including age, sex, tumor location (cardia, fundus, body, antrum, diffuse), tumor grade, tumor stage, lymph node stage, tumor stage, and the ratio of metastatic lymph nodes to total removed lymph nodes (MLR) in patients with gastric adenocarcinoma undergoing curative surgical resection (R0) gastric resection.

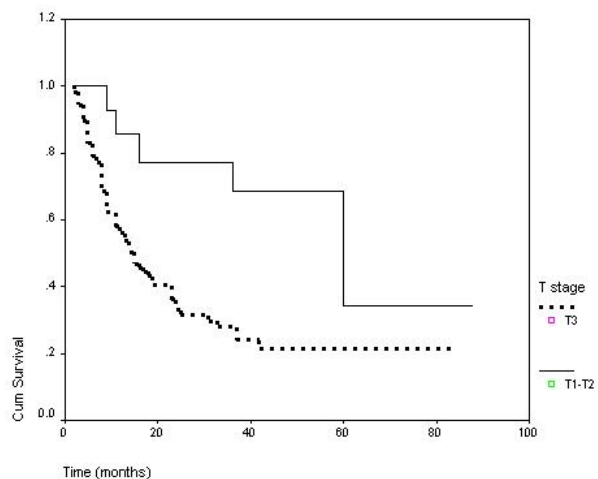
### Materials and Methods

This cohort study has performed on patients with gastric adenocarcinoma in oncology departments, Imam Reza and Omid Hospitals affiliated to Mashhad University of Medical Sciences from 2003 to 2010. Patients who have undergone curative D1 gastrectomy with retrieval of at least 6 lymph nodes have enrolled in this study. We have excluded patients with distant metastases and/or insufficient data regarding their management and follow up. Patients who have received neoadjuvant chemotherapy have excluded from the study.

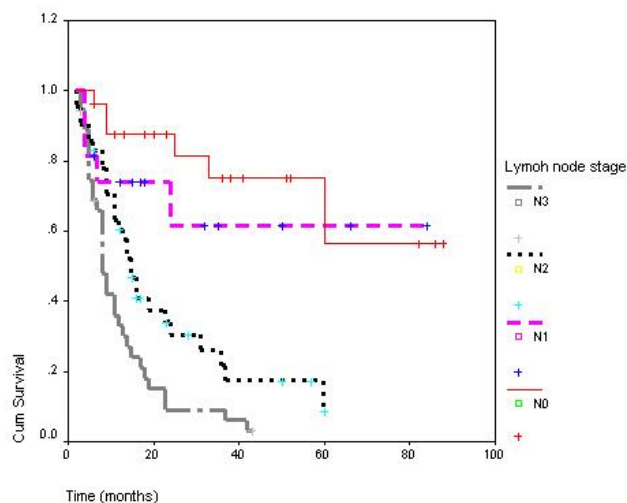
Clinical and pathological information including age, sex, tumor location (cardiac, fundus, body, antrum, diffuse), tumor grade, tumor stage, lymph node stage which have based on UICC/ AJCC, disease stage, the ratio of metastatic lymph nodes to total removed lymph nodes (MLR) ,and then the adjuvant treatment methods have extracted. We have

considered the median MLR to choose a cut-off point for allocation of patients in different groups.

The patients' demographic characteristics have defined using descriptive statistics including central and dispersion indices and distribution frequency, in the form of tables and charts. Kaplan-Meier method has used to measure the survival rates from the surgery time to the death time or the last alive visit. We have used log-rank test for univariate comparison between survival curves and Cox proportional hazards model for multivariate analysis. We have considered P values less than 0.05 as



**Figure 1.** The figure has shown the overall survival rates have stratified by different tumor stages.



**Figure 2.** The figure has shown the overall survival rates have stratified by different lymph node tumor stages.

**Table 1.** Clinical and pathological patients' characteristics

Factor	Number (%)
<b>Age</b>	
≤65	61 (50.4)
>65	60 (49.5)
<b>Sex</b>	
Male	91 (75.2)
Female	30 (24.8)
<b>Pathological subtype</b>	
Intestinal	45 (37.2)
Diffuse	19 (15.7)
Mixed	6 (4.9)
Undefined	51 (42.1)
<b>Tumor grade</b>	
G1	25 (20.6)
G2	58 (47.9)
G3	12 (9.9)
Undefined	26 (21.4)
<b>Tumor location</b>	
Cardia	31 (25.6)
Body	31 (25.6)
Antropyloric	34 (28.1)
Diffuse	17 (14.0)
Undefined	8 (6.6)
<b>Tumor stage</b>	
T1-T2	16 (13.2)
T3	105 (86.7)
<b>Lymph node stage</b>	
N0	28 (23.1)
N1	16 (13.2)
N2	41 (33.8)
N3	36 (29.7)
<b>Disease stage</b>	
IA	2 (1.6)
IB	7 (5.8)
IIA	21 (17.3)
IIB	18 (14.8)
IIIA	37 (30.5)
IIIB	36 (29.7)
<b>MLR</b>	
MLR <sub>0</sub>	28 (23.1)
MLR <sub>1</sub>	31 (25.6)
MLR <sub>2</sub>	62 (51.2)

statistically significant. All statistical analyses have performed by SPSS version 18.

## Results

From a total number of 550 gastric cancer patients who have referred to our institutes between 2003 and 2010, 121 cases were eligible for our study. The median age of patients was 65 (range;

32-89) with 91 males (75.2%) and 30 females (24.8%). The treatment modalities were as follows: 88 total gastrectomy (72.5%), 33 subtotal gastrectomy (27.5%), 70 patients have received combined chemotherapy and radiotherapy (64.8%) and 38 have received chemotherapy alone (35.2%). All chemotherapy regimens have contained Fluoropyrimidines (5-FU or capecitabine). The most common used chemotherapy regimens were ECF

**Table 2.** The correlation between MLR (Metastatic Lymph node Ratio) and some of the pathological factors

Factor	Number	MLR			Chi-Square p-value
		0	>0 – 0.33	>0.33- 1	
<b>Tumor stage</b>					
<b>T1-T2</b>	16	9 (56.3%)	4 (25%)	3 (18.8%)	0.002
<b>T3</b>	105	19 (18.1)	27 (25.7%)	59 (56.2%)	
<b>Grade</b>					
<b>G1</b>	25	6 (24%)	6 (24%)	13 (52%)	0.9
<b>G2</b>	58	11 (19%)	15 (25.9%)	32 (55.2%)	
<b>G3</b>	12	2 (16.7%)	4 (33%)	51 (33.7%)	
<b>Pathological Type</b>					
<b>Intestinal</b>	45	10 (22.2%)	13 (28.9%)	22 (48.9%)	0.7
<b>Diffuse/Mixed</b>	25	4 (16%)	7 (28%)	14 (56%)	

(Epirubicine, Cisplatin, 5FU), 5-FU plus Leucovorine and FLO (5-FU, Leucovorin, Oxaliplatin). The clinical and pathological characteristics of patients have illustrated in Table 1.

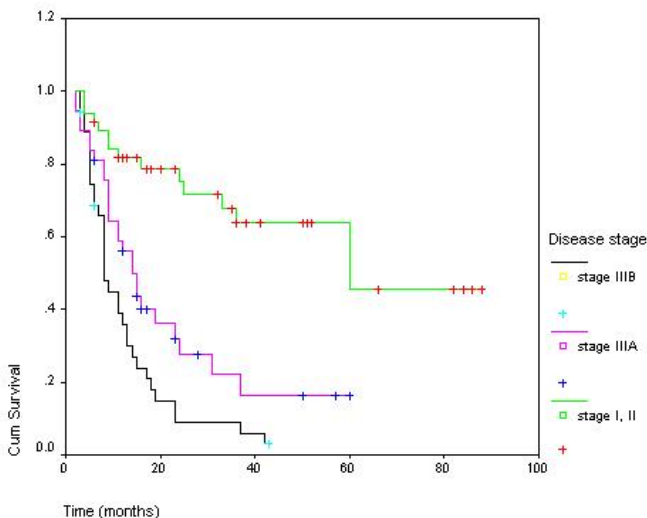
The median number of resected lymph node was 11 (range; 6-44). In 93 patients (76.9%), the obtained lymph nodes were positive for metastases. The median number of metastatic lymph nodes was 4 (range; 0-33). The median MLR was 0.38. Accordingly, our cases have categorized into 3 subgroups (MLR0: 0, MLR1: >0-0.33, MLR2: 0.34-1). MLR0 to MLR2 have found in 28 (23.1%), 31 (25.6%) and 62 (51.2%) cases respectively.

MLR had a significant correlation with tumor depth. MLR2 has found in significantly higher number of patients with T3 as compared to those with T1-2 tumors (59/105; 56.2% versus 3/16;

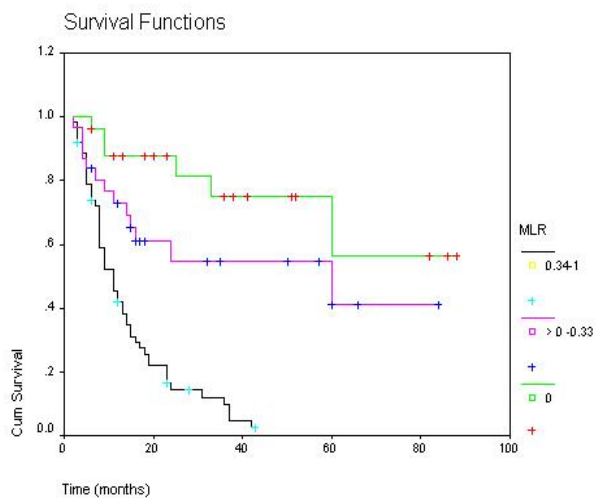
18.7%, p=0.002). In our series, MLR has not associated with tumor type and tumor grade (Table 2).

After a median follow up time of 12 months (range; 2-88 months), 74 patients (61.1%) succumb to the disease. For all patients, the 3-year and 5-year overall survival rates were 33.2% (SD 4.9) and 21% (SD 5.7) respectively with a median overall survival time of 16 months (95% CI: 12-20 months).

As shown in Table 3, factors have been including tumor stage (Figure 1), lymph node stage (Figure 2), disease stage (Figure 3), MLR (Figure 4) and tumor location have affected survival significantly in univariate analysis. Meanwhile, sex, age and tumor grade had no significant impact on survival. In multivariate analysis, MLR have remained significant predictor of survival and



**Figure 3.** The figure has shown the overall survival rates have stratified by different disease stages.



**Figure 4.** The figure has shown the overall survival rates have stratified by different MLR (Metastatic Lymph node Ratio).

**Table 3.** Effects of clinical and pathological characteristics and MLR on prognosis of 121 gastric cancer patients in the univariate analysis

Characteristics	Number	Event number (%)	3-year survival % $\pm$ 1SE	5-year survival % $\pm$ 1SE	Univariate Log-rank p-value	Multivariate Cox-regression
<b>Age</b>					0.57	-
<b><math>\leq 65</math></b>	61	36(59)	3.37 $\pm$ 7.2	21.8 $\pm$ 7		
<b><math>&gt;65</math></b>	60	38(63.3)	1.29 $\pm$ 6.6	19.5 $\pm$ 7		
<b>Sex</b>					0.8	-
<b>Male</b>	91	56 (61.5)	32.5 $\pm$ 6.5	23.4 $\pm$ 6.3		
<b>Female</b>	30	18 (60)	35.1 $\pm$ 10.3	14.1 $\pm$ 11.2		
<b>Tumor grade</b>					0.56	-
<b>G1</b>	25	15 (60)	32.5 $\pm$ 10.6	27.1 $\pm$ 10.1		
<b>G2</b>	58	37 (63.8)	33.5 $\pm$ 7.2	11.8 $\pm$ 9.2		
<b>G3</b>	12	6 (50)	31.7 $\pm$ 17.5	Not reached		
<b>Tumor location</b>					$< 0.01$	0.2
<b>Cardia</b>	31	20 (64.5)	15.5 $\pm$ 9	Not reached		
<b>Body</b>	31	18 (58.1)	35.9 $\pm$ 10.2	Not reached		
<b>Antropyloric</b>	34	16 (47.1)	47.3 $\pm$ 9.9	31.5 $\pm$ 14.5		
<b>Diffuse</b>	17	14 (82.4)	14.7 $\pm$ 9.5	Not reached		
<b>Tumor stage</b>					$< 0.01$	0.5
<b>T1-T2</b>	16	6 (37.5)	68.5 $\pm$ 13	27.8 $\pm$ 5		
<b>T3</b>	105	68 (64.7)	34.3 $\pm$ 18	21.3 $\pm$ 5		
<b>LN stage</b>					$> 0.001$	0.7
<b>N0</b>	28	6 (21.4)	75.1 $\pm$ 10	56.4 $\pm$ 17.9		
<b>N1</b>	16	5 (31.2)	61.5 $\pm$ 14.1	61.5 $\pm$ 14.1		
<b>N2</b>	41	30 (73.2)	21.6 $\pm$ 7.7	8.7 $\pm$ 7.1		
<b>N3</b>	36	33 (91.7)	6 $\pm$ 4.1	Not reached		
<b>Disease stage</b>					$< 0.001$	
<b>I, II</b>	48	15 (31.2)	63.9 $\pm$ 8.5	45.6 $\pm$ 12.4		
<b>IIIA</b>	37	26 (70.3)	22.1 $\pm$ 8.3	16.5 $\pm$ 8.7		
<b>IIIB</b>	36	33 (91.7)	8.9 $\pm$ 4.9	Not reached		
<b>MLR</b>					$< 0.001$	
<b>MLR<sub>0</sub></b>	28	6 (21.4)	75.1 $\pm$ 10	56.3 $\pm$ 18		
<b>MLR<sub>1</sub></b>	31	13 (41.9)	54.8 $\pm$ 10	41.1 $\pm$ 14		
<b>MLR<sub>2</sub></b>	62	55 (88.7)	9.5 $\pm$ 4	Not reached		

proved to be the most important independent prognostic factor.

In sub analysis of 91 patients with less than 15 obtained lymph nodes, MLR was still a significant predictor of survival. In these cases, 3-year survival rates in patients with MLR<sub>0</sub>, MLR<sub>1</sub> and MLR<sub>2</sub> was 78.6% $\pm$ 11%, 53.9% $\pm$ 11.9% and 7.1% $\pm$ 4.5% (p value $<$  0.001).

## Discussion

The prognosis of gastric cancer has significantly associated with pathological characteristics of the disease. The most important recognized prognostic factor in gastric cancer patients is lymph node stage [5]. In this study we have investigated the effect of metastatic lymph ratio (MLR) on survival of patients who have undergone curative R0 resection with at least 6 obtained lymph nodes. Although lymph node stage, tumor stage, disease stage, tumor location and MLR significantly



have affected survival in univariate analysis, only MLR has remained independent prognostic factor in Cox regression multivariate assessment.

Despite limiting our study to operable cases, most patients have diagnosed in stage III in our study. Late diagnosis of advanced disease among the most gastric cancer patients has attributed to lack of specific symptoms during the early stages. Meanwhile, in some nations with extensive screening programs, the disease has diagnosed in earlier stages in a higher number of patients [6-8]. Among 70 cases with defined histological subtypes, 45 cases (64.3%) were intestinal which indicated an epidemic pattern in most cases.

In the current study, with a median number of 11 obtained lymph nodes, 93 patients (76.9%) had metastatic lymph nodes. The median number of obtained lymph nodes was less than that of some other studies [7, 9, 10] and the recommended number has retrieved lymph nodes by UICC / AJCC. In our studies, the relatively low number of examined lymph nodes, at least could be related to not performing extensive lymph node resection partly, as a common practice in our institutes.

There was still no consensus about the cut-off limit for MLR in gastric cancer. Ding and colleagues have designed a 20% cut-off for MLR in gastric cancer patients whose have undergone gastrectomy [10], while Lee et al. has classified MLR into four groups of 0, 0-0.3, 0.3-0.6, and  $\geq 0.6$  [6]. Fukuda and colleagues have classified MLR according to the mean of MLR in patients with metastatic lymph nodes into three groups: 0, 0.01-0.19, and  $\geq 20$  [11].

In a trial that has conducted by Lee SR et al on 370 patients whose have undergone radical surgery, MLR has significantly associated in depth with invasion and the number of metastatic lymph nodes ( $p < 0.001$ ). Patients with higher MLR had significantly lower 5-year overall survival rates ( $p < 0.001$ ). In contrast to the number of metastatic lymph nodes, MLR was an independent prognostic factor in Cox-regression multivariate analysis [7].

In a retrospective study in 2010 by Lee SY et al. in Korea, 342 patients have undergone gastrectomy with negative margins (R0), along with lymph nodes resection, and then without distant metastasis have studied. MLR has classified into four MLR stages including 0, 0-0.3, 0.3-0.6,  $>0.6$ . Age, tumor stage, lymph node stage, MLR, tumor size, type of surgery, and chemotherapy had significant predictor of survival In univariate analysis. However, only MLR, age, tumor size, and

performing chemotherapy have remained independent prognostic factors in multivariate analysis. Among these, MLR was the most important predictive factor for survival [6].

Bacili et al has studied 111 gastric cancer patients who have undergone D2 lymph node resection and then have shown that higher MLR has associated with larger tumors, lymphatic/blood vessel invasion, perineural invasion and advanced stages. In multivariate analysis, UICC/AJCC PN stage, MLR and perineural invasion were significant prognostic factors [9].

In another study that has conducted in China by Ding and colleagues, survival rate of 169 patients with gastric cancer who have undergone D2 gastrectomy has studied. The 5-year overall survival rate of all patients was 29.6%. They have shown that MLR has related to tumor size and depth of sub mucosal invasion. Cumulative survival rates of 70.6% and 12%, have calculated in patients with metastatic lymph node involvement of 1-20% and  $>20\%$  respectively. In their study, MLR counting as 20% was significant predictive of survival in univariate analysis. However, it has failed to remain as an independent factor according to the results of multivariate analysis [10].

In comparison with the results of our study, most previous trials have shown that MLR is an important prognostic factor in patients with gastric cancer who have undergone curative surgery. In many trials including ours, it was the most important independent diagnostic factor in gastric cancer. It has seemed that a cut off level of 0.33 was suitable for categorizing MLR in these patients. MLR could be used as an independent prognostic factor even in cases with insufficient number ( $<15$ ) of obtained lymph node. Finally, although multivariate analysis has shown MLR to be more accurate prognostic factor than staging, study of large sample size with at least 15 nodes evaluation might show a relationship with disease staging.

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## Conflict of Interest

The authors had no conflict of interest in this study.

## Authors' Contribution

Ali Taghizadeh-Kermani and Mohsen Aliakbarian have designed and written this article, Seyede Zeinab Yahouiyani, Mehdi Seilanian Toussi have collected the data, Ali Taghizadeh-Kermani and Mohsen Aliakbarian have analyzed the data. All authors have read and approved the final manuscript.

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