Lymph Node Ratio Predicts Overall Survival in pT4 Gastric Cancer Patients who Underwent Curative Surgery

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Research Article

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Abstract

Background: Lymph node ratio (LNR), the ratio of metastatic lymph nodes to the total number of examined lymph nodes, has been considered a prognostic factor in gastric cancer (GC) patients. However, the predictive values of LNR vary as characteristics of patients are different. We confirmed its prognostic value and investigated the differences between patients with different pathological features.

Methods: Totally, 211 GC patients who underwent curative gastrectomy between October 2004 and November 2016 were retrospectively investigated. Patients were classified into LNR 0, 1 and 2, using cutoff values 0.05 and 0.2. Cutoff values were calculated by Youden index. Relationships between LNR and clinicopathological characteristics were investigated by chi-square test or Fisher's exact test. Survival analysis were based on Cox proportional hazard regression model and Kaplan-Meier method.

Results: LNR were related to tumor size ($p = 0.003$), Lauren classification ($p = 0.007$), grade of differentiation ($p = 0.041$), pT stage ($p = 0.050$) and pN stage ($p < 0.001$). In multivariable analysis, LNR was an independent prognostic factor (HR = 7.023, $p < 0.001$). In stratification analysis, LNR showed independent prognostic value (HR = 4.852, $p < 0.001$) in pT4 patients, but not in pT3 patients ($p = 0.361$) and pT1-2 patients ($p = 0.123$).

Conclusions: LNR is an independent predictor of overall survival in pT4 GC patients who underwent curative surgery.

Background

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related death around the world[1]. Although neoadjuvant therapy has been recommended by many guidelines, surgery with or without adjuvant therapy is still the main treatment in gastric cancer[2]. Lymph node metastasis often show a great predictive value for the prognosis, no matter whether the patients underwent neoadjuvant therapy and adjuvant therapy[3, 4]. Therefore, lymph node status is considered one of the most important prognostic factors in gastric cancer.

Nevertheless, in the AJCC TNM system, only the number of metastatic lymph nodes is considered to determine the pathological lymph node stage (pN)[5]. Although to determine pN stage, at least 16 lymph nodes need to be cleared, some studies supported the number of removed lymph nodes should be larger than 30[6]. Moreover, some studies also found the number of examined lymph nodes is related to the prognosis[7]. These studies hint that not only the number of metastatic lymph nodes is important, the number of retrieved lymph nodes also plays an important role to the prognosis.

Lymph node ratio (LNR) is the ratio of positive lymph nodes to the total lymph nodes removed. It contains information about both metastatic lymph nodes and retrieved lymph nodes. Many studies prove that LNR is related to the prognosis[8, 9] and it could be used to determine the appropriate adjuvant chemotherapy regimen[10, 11]. However, the predictive values of LNR are not the same when other characteristics of

patients are different[12–14], and the cutoff value of LNR is still controversial[15, 16]. Even, in some studies, LNR was not related to the prognosis[17]. Therefore, the aim of this study is to verify the prognostic value of LNR, to add an evidence for the possible cutoff value based on our data, and to explore the differences of the predictive value of LNR among patients with different characteristics.

Methods

1. Patients

Patients who underwent curative resection for gastric cancer between October 2004 and November 2016 at our hospital were identified. Inclusion criteria were the following: (1) pathological confirmed gastric adenocarcinoma; (2) R0 curative gastrectomy with or without adjuvant; (3) no less than a D2 lymph node dissection; Exclusion criteria were (1) identifiable distant metastasis in the liver, peritoneum, and so on; (5) recurrent gastric carcinoma or remnant gastric carcinoma; (6) incomplete information about staging or treatment. After selected, 211 patients were included in this retrospective study.

2. Reevaluation of clinicopathological characteristics

All clinicopathological characteristics about included patients were extracted from our databases. All slices or blocks indicating surgical specimens and lymph nodes were reevaluated by two pathologists who had no knowledge about other information of the patients. Pathological staging was according to 8^{th} American Joint Committee on Cancer (AJCC) guideline.

LNR was defined as the ratio of the number of metastatic regional lymph nodes to the total number of lymph nodes examined. Based on the method of Youden index, the optimal cutoff values of LNR were set as 0.05 and 0.2. Therefore, LNR in this study was divided into three groups, LNR0: LNR less than 0.05; LNR1: LNR more than or equal to 0.05 but less than 0.2; and LNR2: LNR more than or equal to 0.2.

3. Statistical methods

The associations between LNR and other categorical variables were calculated using the chi-square test or Fisher's exact test. Univariable and multivariable analyses for survival were analyzed by Cox proportional hazard regression model. Variables with $p < 0.05$ were considered significant. The Kaplan-Meier method was used to obtain survival curves, and log-rank test was used to compare the differences. The cutoff values of LNR were obtained by Youden index. All patients were followed up every three months during the first two years, every six months for the following three years and yearly thereafter. Overall survival (OS) was defined as the time from the day of operation to the day of death from any cause or last follow-up day. Data was processed by SPSS ver. 25.0 and R 3.6.1 software.

Results

1. Patient characteristics

The information of all 211 patients was listed in **Table 1**. Of all patients, 142 (67.3%) were male and 69 (32.7%) were female. The median age was 59 (range 25 to 84) years. Most tumors (58.3%) were located in the lower third part of the stomach. Totally, 4611 slices were reviewed, including 3978 slices indicating lymph nodes. After reevaluation, 94 patients (44.5%) had no lymph node metastasis (pN0); 35 patients (16.6%) had one to two lymph node metastasis (pN1); 43 patients (20.4%) had three to six lymph node metastasis (pN2); 29 patients (13.7%) had seven to fifteen lymph node metastasis (pN3a); and 10 patients (4.7%) had more than or equal to sixteen lymph node metastasis (pN3b). Regarding to LNR, the numbers of patients in LNR0, 1 and 2 groups were 97, 51 and 63, respectively.

As for other pathological features, only a small percentage of cancers (17.1%) were poorly cohesive carcinoma, i.e. mucous adenocarcinoma (2.4%) and signet ring cell carcinoma (14.7%). Fifty-eight (27.5%) tumors were well differentiated and forty-seven (22.3%) tumors were moderate differentiated. All patients underwent adjuvant therapy, and almost a half of them (46.4%) underwent SOX.

2. Relationships between LNR and other clinicopathological characteristics

The associations between LNR and other clinicopathological characteristics could be seen in **Table 1**. Patients who had a larger tumor tended to have a worse LNR ($p = 0.003$). Patients who had a tumor of diffuse or mixed classification ($p = 0.007$) or had a poor differentiated tumor ($p = 0.041$) also showed a worse LNR. In addition, pathological T stage ($p = 0.050$) and N stage ($p < 0.001$) also showed relationships with LNR (**Table 1**). The adjuvant therapy showed no relationships with LNR ($p = 0.661$) (data not shown).

3. Prognostic value of LNR

The analyses for overall survival were shown in **Table 2.** In the univariable analysis, tumor size (HR = 2.545, $p < 0.001$), Lauren classification (HR = 1.924, $p = 0.016$), pathological T stage (pT) (HR = 5.679, $p = 0.004$), pathological N stage (HR = 16.302, $p < 0.001$) and LNR (HR = 7.023, $p < 0.001$) were related to the prognosis. Because pN and LNR had great collinearity, these two factors were included in the multivariable analysis respectively. In multivariable analysis including pN, pT (HR = 3.602, $p = 0.043$) and pN (HR = 11.986, $p = 0.001$) were independent prognostic factors. Similarly, in multivariable analysis including LNR, pT (HR = 3.694, $p = 0.041$) and LNR (HR = 4.852, $p < 0.001$) were independent prognostic factors (**Table 2**). The survival curves of pN and LNR were shown in **Fig. 1**. Pathological N stage ($p < 0.001$) and LNR ($p < 0.001$) were related to prognosis. In addition, ROC curves of pN stage and LNR were made, and the area under curves were 0.686 and 0.687, respectively, with no statistical significance (data not shown).

4. Stratification analysis on LNR according to pathological T stage

Because pT was also an independent prognostic factor besides pN and LNR, stratification analysis according to pT was performed. The survival curves of LNR stratified by pT were shown in **Fig. 2**. In pT1-2

(p = 0.043) patients and pT4 (p <0.001) patients, LNR was related to overall survival. However, in pT3 patients, LNR was not related to the prognosis (p = 0.374).

Multivariable analyses were performed after stratification (**Table 3**). In pT4 patients, LNR was still an independent prognostic factor (HR = 7.149, p < 0.001). However, in pT3 patients, LNR was no longer an independent prognostic factor (p = 0.361). Instead, tumor size was an independent prognostic factor (HR = 4.914, p = 0.020). In pT1-2 patients, LNR also showed no independent predictive value (p = 0.123) (data not shown).

Discussion

In this study, LNR was a predictor for the prognosis. This result is in line with many other studies. Kano et al.[8] suggested LNR was an independent predictor for the recurrence-free survival; however, their cutoff values of LNR were 0, 0.1 and 0.25. Huang et al.[18] proved that LNR was related to the 5-year OS rates, especially when it was used together with pathological T stage, though they used the cutoff values of 0.03, 0.08, 0.3 and 0.7. In the study published by Hwang et al.[10], LNR was associated with disease-free survival, especially in the stage III patients, based on the cutoff values of 0.1 and 0.25. Bilici et al.[19] also proved that the LNR was a useful indicator to determine the prognosis and recurrence; however their patients were all in pN3 stage, and the cutoff value they used was 0.75.

On the other hand, LNR has the potential to improve the AJCC system. Zhou et al.[20] suggested that LNR had a better predictive value than pN stage. Huang et al.[18] suggested that a modified AJCC system based on LNR had a better prognostic value than the one based on pN stage. Lee et al.[21] and Alatengbaolide et al.[22] suggested that AJCC system based on LNR has better stability than that based on pN stage. Nevertheless, Nakagawa et al.[14] suggested that LNR was not superior to pN stage in evaluating the prognosis, though their study was based on patients with remnant gastric cancer. In our study, the prognostic predictive value of pN stage and LNR had no significant difference, which is similar with the conclusion from Bouliaris et al.[9] study.

Many studies supported that LNR was an important indicator for the choice of appropriate adjuvant chemotherapy regimen[10, 11, 23]. Hwang et al.[10] suggested that if stage III gastric cancer patients with lymphovascular invasion had a high LNR, these patients tended to benefit from platinum-based adjuvant chemotherapy. Another study published by Kim et al.[11] suggested that patients with high LNR tented to have a better prognosis if they underwent adjuvant chemoradiation rather than adjuvant chemotherapy. Shin et al.[23] suggested that patients with a high LNR could benefit more from XELOX over S-1 in adjuvant therapy. However, in our study, there were no associations among LNR and adjuvant therapy.

In addition, LNR showed relationships with other clinicopathological characteristics. LNR was related to tumor location[8, 10], tumor size[24], grade of differentiation[8, 9, 16, 24], pT stage[8–10, 16], TNM stage[9, 10, 16], lymphovascular invasion[8–10, 16] and nervous invasion[10]. In our study, LNR was also related to Lauren classification. To verify this result, more researches based on larger sample size are needed.

There are some limitations in this study. This is a retrospective study, which means potential bias might exist. The sample size is small, which could cause too large or too small statistics and could hinder further hierarchical analysis. The cutoff values were different from other studies, which might hinder the comparison among studies. Nevertheless, this study is based on a certain group of patients, and has proved the predictive value of LNR changes with other characteristics, especially pT stage. Besides, this study adds an evidence to the possible cutoff value, which might contribute to the unification of the LNR.

Conclusions

In conclusion, LNR was an independent prognostic factor for GC patients who underwent curative surgery and adjuvant therapy, especially for patients in pT4 stage.

Abbreviations

GC: gastric cancer; LNR: Lymph node ratio; TNM: tumor-node-metastasis; pT stage: pathological tumor stage; pN stage: pathological lymph node stage; AJCC: American Joint Committee on Cancer; OS: Overall survival.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Faculty of Science Ethics Committee at Shengjing Hospital of China Medical University. The use of hospital databases was approved by the ethics committee. This is a retrospective study and all patients have signed the informed consent prior to treatment. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FY performed the majority of experiments and drafted the manuscript; XY analyzed the data; QL reviewed and revised the manuscript; JW and YC assisted in collected and analyzed the data; DY supervised the study and provided critical revision of the manuscript. All authors have read and approved the manuscript.

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Tables

Table 1 Patients characteristics according to lymph node ratio (LNR)

Variable	LNR0 (n=97) %	LNR1 (n=51) %	LNR2 (n=63) %	P	No. (%)
Gender				0.260	
Male	60 (28.4)	38 (18.0)	44 (20.9)		142 (67.3)
Female	37 (17.5)	13 (6.2)	19 (9.0)		69 (32.7)
Age (yr)				0.225	
50	22 (10.4)	7 (3.3)	17 (8.1)		46 (21.8)
≥50	75 (35.5)	44 (20.9)	46 (21.8)		165 (78.2)
Tumor size (cm)				**0.003**	
<5	66 (31.3)	22 (10.4)	29 (13.7)		117 (55.5)
≥5	31 (14.7)	29 (13.7)	34 (16.1)		94 (44.5)
Histological type				0.744	
Adenocarcinoma	80 (37.9)	44 (20.9)	51 (24.2)		175 (82.9)
Poorly cohesive carcinoma	17 (8.1)	7 (3.3)	12 (5.7)		36 (17.1)
Lauren classification				**0.007**	
Intestinal	56 (26.5)	28 (13.3)	21 (10.0)		105 (49.8)
Diffuse or Mixed	41 (19.4)	23 (10.9)	42 (19.9)		106 (50.2)
Grade of differentiation				**0.041**	
Well or Moderate	53 (25.1)	29 (13.7)	23 (10.9)		105 (49.8)
Poor	44 (20.9)	22 (10.4)	40 (19.0)		106 (50.2)
pT				**0.050**	
1-2	29 (13.7)	6 (2.8)	9 (4.3)		44 (20.9)
3	26 (12.3)	20 (9.5)	23 (10.9)		69 (32.7)
4	42 (19.9)	25 (11.8)	31 (14.7)		98 (46.4)
pN				**<0.001**	

0	94 (44.5)	0 (0.0)	0 (0.0)	94 (44.5)
1	3 (1.4)	32 (15.2)	0 (0.0)	35 (16.6)
2	0 (0.0)	18 (8.5)	25 (58.1)	43 (20.4)
3a	0 (0.0)	1 (0.5)	28 (13.3)	29 (13.7)
3b	0 (0.0)	0 (0.0)	10 (4.7)	10 (4.7)

Note: LNR, lymph node ratio; UGEJ, upper third and gastroesophageal junction

Table 2 Cox proportional hazard regression model for overall survival

	Univariable analysis		Multivariable analysis (pN)		Multivariable analysis (LNR)	
Variable	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Gender (Female)	0.661 (0.366, 1.193)	0.169	0.768 (0.385, 1.533)	0.454	0.834 (0.420, 1.655)	0.604
Age (≥50yr)	1.014 (0.512, 2.010)	0.968	1.123 (0.516, 2.443)	0.771	1.063 (0.494, 2.287)	0.875
Tumor location		0.457		0.276		0.364
UGEJ	1		1		1	
Middle third	0.497 (0.212, 1.166)	0.108	0.745 (0.309, 1.795)	0.512	0.633 (0.265, 1.513)	0.303
Lower third	0.699 (0.344, 1.421)	0.322	1.474 (0.685, 3.172)	0.321	1.180 (0.555, 2.508)	0.668
Diffuse	0.763 (0.097, 6.009)	0.797	1.057 (0.126, 8.900)	0.959	0.802 (0.098, 6.581)	0.838
Tumor size (≥5cm)	2.545 (1.498, 4.323)	**<0.001**	1.404 (0.744, 2.650)	0.295	1.593 (0.854, 2.972)	0.143
Histological type (Poorly cohesive carcinoma)	1.126 (0.569, 2.228)	0.733	1.113 (0.488, 2.541)	0.799	0.966 (0.436, 2.138)	0.932
Lauren classification (Diffuse or Mixed)	1.924 (1.129, 3.278)	**0.016**	2.323 (0.843, 6.403)	0.103	2.409 (0.921, 6.302)	0.073
Grade of differentiation (Poor)	1.651 (0.978, 2.786)	0.060	0.542 (0.192, 1.532)	0.248	0.594 (0.224, 1.573)	0.295
pT		**0.004**		**0.043**		**0.041**
1-2	1		1		1	
3	5.852 (1.926, 17.781)	**0.002**	2.348 (0.724, 7.615)	0.155	2.470 (0.768, 7.945)	0.129
4	5.679 (2.015, 16.004)	**0.001**	3.602 (1.207, 10.745)	**0.022**	3.694 (1.242, 10.985)	**0.019**

pN		**<0.001**		**0.001**		
0	1		1			
1	2.106 (0.844, 5.258)	0.111	1.896 (0.689, 5.216)	0.216		
2	4.913 (2.395, 10.077)	**<0.001**	3.553 (1.558, 8.101)	0.003		
3a	5.995 (2.659, 13.518)	**<0.001**	4.859 (1.914, 12.339)	**<0.001**		
3b	16.302 (5.787, 45.924)	**<0.001**	11.986 (3.346, 42.938)	**<0.001**		
LNR		**<0.001**				**<0.001**
0	1				1	
1	2.964 (1.399, 6.283)	**0.005**			2.106 (0.913, 4.857)	0.081
2	7.023 (3.557, 13.868)	**<0.001**			4.852 (2.264, 10.397)	**<0.001**

Note: LNR, lymph node ratio; UGEJ, upper third and gastroesophageal junction

Table 3 Stratification analysis according to pathological T stage

	Multivariable analysis (pT3)		Multivariable analysis (pT4)	
Variable	OR (95%CI)	P	OR (95%CI)	P
Gender (Female)	1.215 (0.353, 4.188)	0.758	0.832 (0.321, 2.161)	0.706
Age (≥50yr)	0.381 (0.094, 1.539)	0.175	1.512 (0.499, 4.581)	0.464
Tumor location		0.453		0.186
UGEJ	1		1	
Middle third	1.859 (0.153, 22.620)	0.627	0.366 (0.128, 1.046)	0.061
Lower third	4.325 (0.461, 40.578)	0.200	0.862 (0.329, 2.257)	0.762
Diffuse	*	0.990	1.970 (0.204, 19.022)	0.558
Tumor size (≥5cm)	4.914 (1.289, 18.726)	**0.020**	0.787 (0.333, 1.858)	0.585
Histological type (Poorly cohesive carcinoma)	1.023 (0.178, 5.874)	0.980	0.895 (0.327, 2.446)	0.829
Lauren classification (Diffuse or Mixed)	1.881 (0.302, 11.730)	0.499	3.580 (0.963, 13.305)	0.057
Grade of differentiation (Moderate or Poor)	0.265 (0.043, 1.651)	0.155	0.646 (0.166, 2.505)	0.527
LNR		0.361		**<0.001**
0	1		1	
1	1.083 (0.189, 6.214)	0.929	3.573 (1.086, 11.758)	**0.036**
2	2.374 (0.513, 10.974)	0.268	7.149 (2.689, 20.470)	**<0.001**

Note: LNR, lymph node ratio; UGEJ, upper third and gastroesophageal junction; *too small to record

Figures

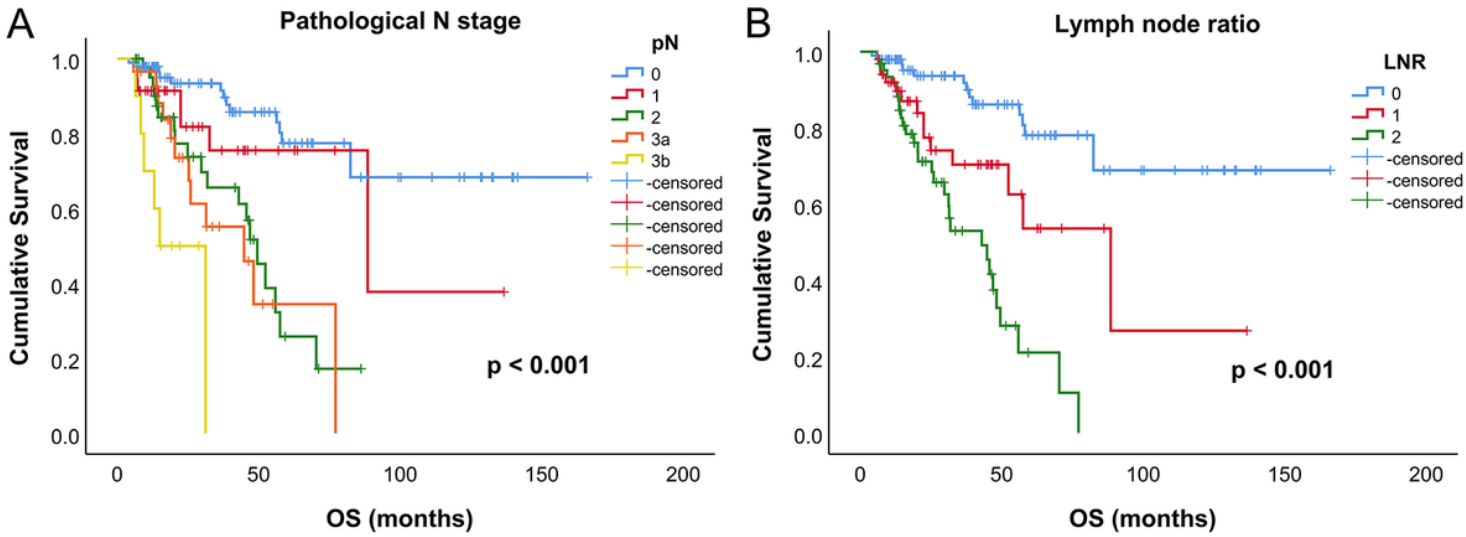

Figure 1

Kaplan–Meier curves for (A) pathological N stage (pN) and (B) lymph node ratio (LNR).

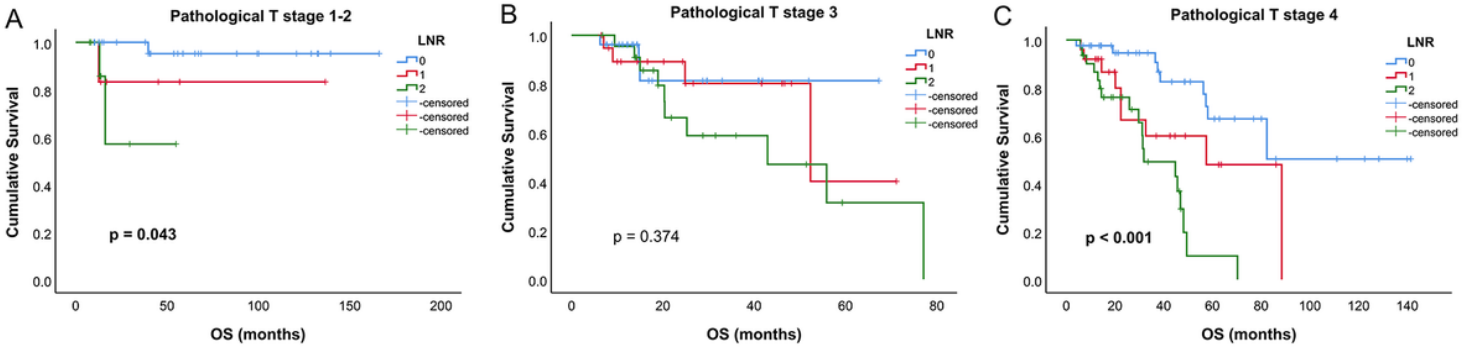

Figure 2

Kaplan–Meier curves in stratified analysis. (A) pathological T stage (pT) 1-2; (B) pT3; and (C) pT4.