

Lymph node ratio is an independent prognostic factor for patients with Siewert type II adenocarcinoma of esophagogastric junction: results from a 10-year follow-up study

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Research

Keywords: Adenocarcinoma of the esophagogastric junction, Lymph node ratio, Number of dissected lymph nodes, Prognosis

Posted Date: April 13th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-21640/v1>

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Version of Record: A version of this preprint was published at Journal of Gastrointestinal Cancer on September 21st, 2020. See the published version at <https://doi.org/10.1007/s12029-020-00468-y>.

Abstract

Background Emerging evidences suggest that lymph node ratio (LNR), the number of metastatic lymph node (LN) to the total number of dissected lymph nodes (NDLN), may predict survival in multiple types of solid tumor. However, the prognostic role of LNR in adenocarcinoma of the esophagogastric junction (AEG) remains uninvestigated. The study is intended to determine the prognostic value of LNR in the patients with Siewert type II AEG. Methods A total of 342 patients with Siewert type II AEG who underwent R0 resection were enrolled in this study. The optimal cut-off of LNR was stratified into tertiles using X-tile software. The log-rank test was used to evaluate the survival differences, and multivariate Cox regression analysis were performed to determine the independent prognostic variables. Results The optimal cut-off of LNR were classified as LNR = 0, LNR between 0.01 and 0.40 and LNR > 0.41. Patients with high LNR had a shorter 5- and 10-year disease-specific survival (DSS) rate (8.5%, 1.4%) compared with those with moderate LNR (20.4%, 4.9%) and low LNR (58.0%, 27.5%) ($P < 0.001$). Multivariate Cox regression analysis indicated that LNR was an independent factor for DSS after adjusting for confounding variables ($P < 0.05$). Furthermore, after stratification by NDNLN between NDNLN < 15 group and NDNLN \geq 15 group, the LNR remained a significant predictor for DSS ($P < 0.05$). Conclusions LNR is an independent predictor for DSS in patients with Siewert type II AEG regardless of NDNLN. Patients with higher LNR have significantly shorter DSS.

Background

The morbidities of esophagogastric junction carcinoma (EGJ) have dramatically increased in recent decades [1–3]. EGJ is characterized by pathologically heterogeneous tumors developing in the border between the esophageal squamous epithelium and gastric adenomatous epithelium, and includes cardiac adenocarcinoma, adenocarcinoma of the distal esophagus, and squamous cell carcinoma of the distal esophagus [4]. Among the EGJ, adenocarcinoma of esophagogastric junction (AEG) is the most common pathological type [3]. Due to its unique anatomic position, special gene expression profile and aggressive behavior, AEG is gaining more and more attention as an independent disease [5, 6]. At present, surgery remains the mainstay for resectable AEG [7], but the overall efficacy is not satisfactory in patients with advanced stage diseases [8]. Currently, lymph node (LN) status is a stronger prognostic factor for survival in AEG, and the absolute number of positive LNs is used for determining nodal staging. However, a number of investigators have argued that the current nodal staging based on the positive LNs could be influenced by total number of dissected lymph nodes (NDLN), and probably leading to stage migration [9, 10]. Therefore, it is imperative to identify a more reliable prognostic marker to tailor subsequent chemotherapy or radiation therapy.

Increasing evidences have suggested that lymph node ratio (LNR), the count of positive LN to the NDNLN, may affect the prognosis in a variety of solid carcinomas [11, 12], including esophageal carcinoma [9, 13] and gastric cancer [10, 14]. Up to now, the LNR has not been evaluated specifically for Siewert type II AEG, and it's crucial to identify optimal indicator with reliable prognostic information. The purpose of this study was to evaluate the prognostic value of LNR in patients with Siewert type II AEG.

Materials And Methods

Patients

All patients including in this study admitted the Cancer Hospital of Shantou University Medical College. According to the Siewert classification system, AEG can be categorized into three types as follows: AEG type I, the tumor center located 1–5 cm above the gastric cardia; AEG type II, the tumor center between 1 cm above and 2 cm below the gastric cardia; and AEG type III, the tumor center located 2–5 cm below the gastric cardia [15, 16]. In our hospital, Siewert type I AEG and Siewert type III AEG were classified as esophageal cancer and gastric cancer, respectively. Therefore, all patients enrolled in this study were diagnosed with Siewert type II AEG. The exclusion criteria as follow: (1) Patients rejected further therapy after diagnosis; (2) Patients with distant metastasis; (3) Patients received neoadjuvant chemotherapy or radiation therapy before surgery; (4) Patients without R0 resection. From January 1th, 2000 to December 31th, 2010, 342 of patients with Siewert type II AEG were eligible for inclusion. The primary tumor size (T), regional lymph node (N), distant metastasis (M) and the pTNM staging for each patient were according to 8 edition of American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) [17]. Tumor histologic type and differentiation were also evaluated according to the AJCC/UICC classification [17]. Routine laboratory tests for liver and kidney function, chest electrocardiography, esophageal barium meal examination, and chest and abdomen computed tomography scans were performed in order to exclude surgery contraindications. This study was conducted with the approval of the Ethics Committee and the Institutional Review Board of the Cancer Hospital of Shantou University Medical College (IRB serial number: # 04–070).

Follow-up

The primary outcome of this study was disease-specific survival (DSS), which was defined as the duration from the date of cancer diagnosis to cancer-associated death. The postoperative follow-up was carried out by regular out-patient visit and telephone interview. The endpoint time was December 31th, 2018, with a median follow-up of 26 months (ranging from 2 to 201 months) and a total of 279 (81.6%) deaths. Patients that died of non-cancer-related causes, as well as those that were lost to follow-up, were also included in the survival analysis, but the information regarding the mortality of these patients was considered as censored data.

Statistical analysis

The distribution of continuous variables was examined using the Mann-Whitney U test. Chi-square or Fisher's exact test were used to compare nominal data. X-tile software (version 3.6.1) was applied to determine the optimal cut-off for LNR based on minimal *P*-value method[18]. Survival analysis was examined by Kaplan–Meier plots and the log-rank test. Univariate analysis was performed to identify potential prognostic factors. Then, multivariate Cox proportional hazard analysis was used to explore independent prognostic factors that were statistically significant ($P < 0.10$) and clinically meaningful in the univariate analysis. Forward Stepwise selection with a likelihood-ratio test was performed to

determine variables for the Cox regression analysis. SPSS statistical software (version 18.0, SPSS Inc., Chicago, IL, USA) was used for all the analyses. The *P* value, based on two-sided test, less than 0.05 was considered as statistically significant.

Results

Patients clinicopathological characteristics

The 342 patients' demographics and clinicopathological characteristics were summarized in the Table S1 (see Additional file 1). There were 298 men (87.1%) and 44 women (12.9%) with a median age of 69.5 (range 39 to 82) years. The Median lesion length was 50 mm (range 10 to 120). There were 30 (8.8%) of patients were T1-2, 172 (50.3%) of patients were T3, 140 (40.9%) of patients were T4. Concerning the N stage, 105 (30.7%) of patients were N0, 68 (19.9%) of patients were N1, 118 (34.5%) of patients were N2, 51 (14.9%) of patients were N3. Of them, the median number of positive lymph nodes was 2, rang 0 to 28; and the median NDLN was 9, rang 1 to 52. According to the pTNM stage of AJCC/ UICC 8th edition [17], 18 (5.3%) of patients were stage I, 57 (16.7%) of patients were stage II, 182 (53.2%) of patients were stage III, 85 (24.8%) of patients were stage IV. The majority of patients were diagnosed with adenocarcinoma and mucinous adenocarcinoma, accounted 79.5% and 12.6%, respectively. Among the 342 patients, 317 (92.7%) patients underwent subtotal esophagectomy with partial gastrectomy, 25 (7.3%) patients underwent total gastrectomy with partial esophagectomy. 92 (26.9%) patients received either adjuvant chemotherapy or radiotherapy.

Univariate survival analysis on disease-specific survival

According to the optimal cut-off analysis using X-tile software [18], 0 and 0.40 were applied as the optimal cut-off value for LNR (Fig. 1). Patients with high LNR (LNR > 0.40) had a shorter 5- and 10-year DSS compared with those in moderate (LNR between 0.01 to 0.40) and low LNR (LNR = 0) groups. The corresponding 5- and 10-year DSS were 8.5%, 20.4%, 58.0% and 1.4%, 4.9%, 27.5%, respectively ($P < 0.001$; Table 1).

As shown in Table 1, Kaplan-Meier analysis showed that the patient age, tumor histopathological type, tumor differentiation, tumor Bormann's type, tumor lesion length, and T stage, N stage, pTNM stage and surgery procedure were significantly associated with DSS ($P < 0.05$). No significant difference was observed in the association between DSS and patient's gender, whether having received chemotherapy or radiotherapy.

Multivariate Cox regression hazards regression analysis

Based on the above univariate analysis, the impact of patient age, tumor histopathological type, tumor differentiation, tumor Bormann's type, tumor lesion length, T stage, N stage, pTNM stage, LNR and surgery procedure on DSS was further tested by multivariable analysis (Table 2). Finally, patient's age, tumor lesion length, pTNM stage and LNR were significantly associated with DSS in multivariate Cox regression analysis (Table 2). Patients in the group of LNR = 0 had a longer DSS. Compared to the group

of LNR = 0, patient with moderate LNR ($0 < \text{LNR} \leq 0.4$) had a 1.64-fold increased risk of cancer-related death (HR = 1.64; 95% CI, 1.04–2.58; $P = 0.034$), and patient with high LNR ($\text{LNR} > 0.4$) had a 2.61-fold increased risk of cancer-related death (HR = 2.61; 95% CI, 1.62–4.20; $P = 0.001$).

Multivariate survival analysis on DSS by stratification of the number of dissected lymph nodes

The NCCN guidelines recommends that at least 15 lymph nodes should be removed for adequate nodal staging [19]. The NDLN is a most important factor associated with LNR. Therefore, we investigated whether the LNR was still associated with DSS by stratifying patients into two groups, $\text{NDLN} < 15$ and $\text{NDLN} \geq 15$. As shown in the Table S2 (see Additional file 2), there were significantly difference on tumor differentiation, tumor length, T stage, N stage, LNR, number of positive lymph node, number of resected lymph nodes, pTNM stage, chemoradiation and surgery procedure between the subgroup of $\text{NDLN} < 15$ and $\text{NDLN} \geq 15$. More patients had advanced tumor stage, poor tumor differentiation, and having received chemotherapy or radiation in the subgroup of $\text{NDLN} \geq 15$. In addition, more patients underwent total gastrectomy with partial esophagectomy in the subgroup of $\text{NDLN} \geq 15$ (Table S1, see Additional file 1). Furthermore, the DSS in the subgroup of $\text{NDLN} < 15$ was longer than the subgroup of $\text{NDLN} \geq 15$ (Fig. S1, see Additional file 3). However, the results of multivariate Cox regression analysis demonstrated that LNR was significantly associated with DSS both on the subgroup of $\text{NDLN} < 15$ and $\text{NDLN} \geq 15$ (Table 3). In the subgroup of $\text{NDLN} < 15$, the 5- and 10-year DSS were 58.1%, 15.4%, 11.1% and 31.2%, 5.9%, 2.2% for patients with LNR = 0, $0.01 < \text{LNR} \leq 0.40$ and $\text{LNR} > 0.4$, respectively (Fig. 2a; $P < 0.001$). In the subgroup of $\text{NDLN} \geq 15$, the 5-year DSS were 56.7%, 25.6% and 3.6% for patients with LNR = 0, $0.01 < \text{LNR} \leq 0.40$ and $\text{LNR} > 0.4$, respectively (Fig. 2b; $P < 0.001$).

Discussion

The involved LN is recognized to be a vital prognostic factor for predicting patient's survival after the operation of gastrointestinal cancer. However, the accuracy of predicting patient's prognosis that harvested sufficient number of suspected metastatic LNs is markedly higher than those without adequate resection of potential involved LNs. A number of investigators have dedicated to identify and develop alternative reliable survival predicting factors or models for patients with gastrointestinal cancer, particularly after removal of the tumor, which could outperform the traditional pTNM staging method [20–22]. In this study, we defined the optimal cut-off of LNR as LNR = 0, LNR between 0.01 and 0.40 and $\text{LNR} > 0.41$ using X-tile software [18]. The 5- and 10-year of DSS in the patients with high, moderate and low LNR were 8.5%, 20.4%, 58.0% and 1.4%, 4.9%, 27.5%, respectively. We also demonstrated that patients age, tumor lesion length, pTNM stage and LNR were independent prognostic factors for DSS. Furthermore, after stratification by NDLN into subgroups of $\text{NDLN} < 15$ and $\text{NDLN} \geq 15$, the LNR remained a significant predictor for DSS. Patients with the high LNR had a shorter 5- and 10-year DSS compared with those in the moderate LNR and low LNR groups.

The TNM staging system predicts survival according to the extent of local involvement of primary tumor, as well as the presence or absence of regional or distant metastasis. However, the adequacy of the current TNM staging system for AEG is increasingly being questioned [23]. The significance of the LNR for predicting AEG prognosis has been described in several studies [24, 25]. Sisic and colleagues also demonstrated that the N stage does not prognosticate survival for preoperatively treated patients, while the prognostic role of the LNR remains significant after neoadjuvant treatment [24].

The parameter of LNR combines the number of involved LNs with the absolute NDLN is in fact particularly appealing. The key merit of LNR is that it can summarize the information reflecting both tumor biology (the number of involved LNs) and treatment modalities (the DNLN) [26], with features of becoming a better indicator to predict the prognosis of patients with AEG. A recent study comprised of 735 patients from the Surveillance, Epidemiology, and End Results database supported that LNR incorporating with a continuous variable, was better than N staging for prognostic prediction of AEG [25]. In line with their results, our study showed that LNR and pTNM stage, but not N stage, were independent prognostic factor for DSS. Therefore, the application of LNR might reduce the stage migration, and provide more prognostic information to overcome limitations of current staging systems.

The best cut-off for LNR in AEG remains undetermined presently. Most published studies on optimal cut-off of LNR values used an arbitrary calculation, mean values, or quartiles to discriminate patient groups based on their prognosis [22, 24, 25, 27]. In this study, we determined the optimal cut-off using X-tile program. Log-rank statistics was used to calculate the minimum *P* values in this program, which can minimize the loss of information from multiple testing through cross-validation and control the inflated type I error [18]. Obviously, it is more appropriate and reliable from a methodological and statistical point of view. In this study, the continuous variate of LNR were classified trichotomy as LNR = 0, LNR between 0.01 and 0.40, and > 0.41. Our results showed that LNR was associated with DSS regardless the number of harvesting LNs. A recent study classified LNR into LNR = 0, $0 < \text{LNR}_2 \leq 0.125$, $0.125 < \text{LNR}_3 \leq 0.425$, and $\text{LNR}_4 > 0.425$ using X-tile software [21], and suggested that LNR was a unique prognostic factor for survival. But their results had no subgroup analysis further. Another study using previous published cut-off value stratified the LNR into LNR = 0, LNR less than 0.30, LNR between 0.31 to 0.60 and LNR > 0.60 [26], their result identified LNR as an essential survival predictor. However, further analysis showed that the LNR had no significance for prognosis in the subgroup of NDLN < 15. Therefore, the optimal cut-off value of LNR in this study still need further validation.

The number of positive LNs identified may depend on the NDLN, while the value of LNR highly depended on both the positive harvesting LNs and NDLN. Accurate evaluation of LN metastasis and NDLN not only leads to appropriate staging but also reliably predicts prognosis [23, 28]. Incorrect assessment of the LNR could result in insufficient NDLN, therefore, causing an inaccurate prognostic assessment. The NCCN guidelines recommendation for operable patients with AEG demonstrated that at least 15 LNs should be removed for adequate nodal staging [19].

Categorization of LNR could probably be affected by the extent of LN dissection and the stage migration phenomenon, particularly in cases with fewer than 15 examined LNs [29]. Therefore, we performed a subgroup analysis to demonstrate whether the value of LNR was still associated with DSS in the subgroup of $NDLN < 15$ and $NDLN \geq 15$. Interestingly, the results of multivariate Cox regression analysis demonstrated that LNR was still associated with DSS both on the subgroup of $NDLN < 15$ and $NDLN \geq 15$. This maybe partly due to LNR incorporates not only the nodal burden and cancer spread but also the extent and quality of surgical staging. Therefore, LNR maybe more meaningful for discriminating subsets of patients with similar prognosis.

The number of LNs harvested affecting the prognosis is a controversial topic. It is reasonable to hypothesize that a higher NDLN is associated with a better clearance of occult LN metastasis. This hypothesis is corroborated by several studies that patients with pN0 Siewert type II EGJ had a survival benefit from harvesting more than 15 of LNs dissection [30, 31]. The NDLN might improve the patient survival, but possibly lead to increased morbidity and mortality. In particular, a variety of comparative studies between West and East have demonstrated that no superior survival rates were observed in more extensive lymphadenectomy [32–34].

More recently, a study by Cao and colleagues indicated that the survival between the patients with $NDLN < 15$ and $NDLN \geq 15$ had no significant difference [35]. This perspective was supported by several retrospective studies, which proposed that the NDLN had no impact on overall survival, while a lower LNR was connected to favorable survival [9, 24]. Inconsistent with their results, our study showed that the DSS in the subgroup of $NDLN < 15$ was better than the subgroup of $NDLN \geq 15$. The reason for this phenomenon may due to more patients had higher LNR, advanced tumor stage, poor tumor differentiation in the subgroup of $NDLN \geq 15$, which contributed to the poor survival. Based on this situation, it may reasonable to propose a viewpoint that tailor a lymphadenectomy according to T- and N-stage for reducing complications in individual would be preferable. Future treatment tactics may include accurate pre-operative assessment of the TNM staging to design an optimal surgical approach. Besides, discovering new biomarkers to locate metastatic nodes or developing novel sentinel node tracing techniques might be considered in future research [36, 37].

There are a couple of limitations in our study. Firstly, it was a retrospective study from a single institution, which may have biases such as absence of random assignment and patient selection. Therefore, validation of our findings in another cohort is warranted. Secondly, the extent of LN dissection was not uniform due to our study spanned over a decade during 2000 to 2010, which the surgical paradigm might had shifted. However, we incorporated the LNR information in case of limited LN dissection, which may compensate the shortage of this situation [38]. Finally, adjuvant chemotherapy or radiation were difficult to finish due to more complications and higher recurrence rate appeared after invasive surgery [39, 40], particular for elderly patients. This may compromise the survival result. But our result suggested that more attention should be pay on these patients with higher LNR, since them may be benefit from treating with aggressive adjuvant chemotherapy [41].

Conclusion

In summary, our study suggests that LNR provides reliable prognostic information in patients with Siewert type II AEG, regardless of the NDLN. Patients with higher LNR had shorter DSS. LNR can reflect the tumor aggressiveness and is not significantly affected by the extent of LN dissection.

Abbreviations

AEG: Adenocarcinoma of the esophagogastric junction; AJCC: American Joint Committee on Cancer; CI: Confidence interval; DSS: Disease-specific survival; EGJ: Esophagogastric junction carcinoma; HR: Hazard risk; LN: Lymph node; LNR: Lymph nodes ratio; NDLN: Number of dissected lymph nodes; UICC: Union for International Cancer Control

Declarations

Funding

This work was supported by the Natural Science Foundation of Guangdong Province, China (Grant No.2018A030313562), and by the Science and Technology Project of Shantou, China (Grant No. 190816095262235, No.190819145262877 and No. 170828211930352).

Availability of data and materials

Please contact the author for data requests.

Authors' Contributions

Conception and study: Yuling Zhang, Chunfa Chen and De Zeng; Acquiring data: Yuling Zhang and Ditian Liu; Statistical analysis: Yuling Zhang, Ditian Liu and Chunfa Chen; Drafting article and critical revision of article: Chunfa Chen and De Zeng. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

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Tables

Table 1 Correlation of characteristics by univariate survival analysis

Characteristics	No. of patients (%) (n = 342)	Median survival (Months) [95% CI]	5 years' survival rate (%)	10 years' survival rate (%)	P value
Age (years)					< 0.001
< 70	171 (50.0)	35 (28-41)	34.6	17.3	
≥ 70	171 (50.0)	24 (20-27)	21.3	3.8	
Gender					0.303
Male	298 (87.1)	29 (24-33)	28.5	10.9	
Female	44 (12.9)	23 (15-30)	24.4	11.0	
Histopathology					0.034
Adenocarcinoma	272 (79.5)	30 (25-34)	30.6	13.3	
Mucinous adenocarcinoma	43 (12.6)	21 (16-25)	14.7	0.0	
Adeno-squamous carcinoma	16 (4.7)	23 (9-36)	18.8	0.0	
Other types	11 (3.2)	40 (8-71)	30.0	0.0	
Differentiation					0.001
High	16 (4.7)	75 (45-103)	65.6	24.9	
Moderate	135 (39.5)	38 (31-44)	36.3	13.3	
Poor	191 (55.8)	24 (21-26)	18.8	8.2	
Bormann's type					< 0.001
Type I	32 (9.4)	39 (33-44)	26.3	21.9	
Type II	94 (27.5)	41 (25-56)	40.1	23.1	
Type III	204 (59.6)	24 (21-26)	23.4	4.6	
Type IV	12 (3.5)	17 (3-61)	16.7	8.3	
Lesion length (mm)					< 0.001
≤ 50	176 (51.5)	40 (31-48)	37.7	19.4	
> 50	166 (48.5)	24 (21-26)	17.6	2.2	
T stage					< 0.001
T1-2	30 (8.8)	89 (62-115)	71.3	34.1	
T3	172 (50.3)	31 (24-37)	28.4	9.4	
T4	140 (40.9)	24 (20-27)	18.2	8.1	
N stage					< 0.001
N0	105 (30.7)	70 (58-81)	57.4	27.2	
N1	68 (19.9)	25 (14-35)	18.7	8.0	

N2	18 (5.3)	24 (20-27)	16.6	0.0	
N3	51 (14.9)	20 (15-24)	6.1	0.0	
LNR					<
					0.001
LNR = 0	104 (30.4)	70 (58-81)	58.0	27.5	
0 < LNR ≤ 0.4	129 (37.7)	27 (22-31)	20.4	4.9	
LNR > 0.4	109 (31.9)	20 (14-25)	8.5	1.4	
pTNM stage					<
					0.001
I	18 (5.3)	139 (74-203)	94.4	53.9	
II	57 (16.7)	60 (31-88)	49.4	19.6	
III	182 (53.2)	29 (23-34)	24.7	8.6	
IVA	85 (24.8)	19 (15-22)	6.0	2.0	
Chemoradiotherapy					0.123
Yes	92 (26.9)	38 (29-46)	33.3	4.0	
No	250 (73.1)	26 (22-29)	26.0	12.7	
Surgery procedure					0.018
Subtotal esophagectomy with partial gastrectomy	317 (92.7)	29 (24-33)	29.4	11.5	
Total gastrectomy with partial esophagectomy	25 (7.3)	20 (13-26)	9.0	4.5	

LNR lymph nodes ratio

Table 2 Multivariate prognostic analysis by the Cox proportional hazard regression

Characteristics	HR (95% CI)	P value
Age (years)		
< 70	1	
≥ 70	1.89 (1.48-2.41)	< 0.001
Histopathology		
Adenocarcinoma		
Mucinous adenocarcinoma		
Adeno-squamous carcinoma		
Other types		
Differentiation		
High		
Moderate		
Poor		
Bormann's type		
Type I		
Type II		
Type III		
Type IV		
Lesion length (mm)		
≤ 50	1	
> 50	1.32 (1.03-1.71)	0.028
T stage		
T1-2		
T3		
T4		
N stage		
N0		
N1		
N2		
N3		
LNR		
LNR = 0	1	
0 < LNR ≤ 0.4	1.64 (1.04-2.58)	0.034
LNR > 0.4	2.61 (1.62-4.20)	< 0.001
pTNM stage		
I	1	
II	2.27 (1.06-4.86)	0.036
III	2.29 (1.02-5.15)	0.044

IVA	4.20 (1.76-10.03)	0.001
Surgery procedure		
Subtotal esophagectomy with partial gastrectomy		
Total gastrectomy with partial esophagectomy		

CI confidence interval, *LNR* lymph nodes ratio, *HR* hazard risk

Table 3 Uni- and Multi-variate prognostic analysis of subgroup between $NDLN < 15$ and $NDLN \geq 15$

Characteristic	NDLN < 15				NDLN ≥ 15			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age (years)								
< 70	1		1		1			
≥ 70	2.13 (1.57- 2.89)	< 0.001	2.13 (1.55- 2.93)	< 0.001	0.95 (0.65- 1.40)	0.801		
Gender								
Male	1				1			
Female	1.10 (0.69- 1.76)	0.661			1.36 (0.75- 2.46)	0.250		
Lesion length (mm)								
≤ 50	1				1			
> 50	1.89 (1.38- 2.58)	< 0.001			1.46 (0.99- 2.15)	0.053		
T stage								
T1-2	1				1			
T3	2.16 (1.43- 3.25)	0.003			2.72 (1.19- 6.18)	0.109		
T4	2.47 (1.59- 3.84)	0.001			4.12 (1.781- 9.52)	0.044		
N stage								
N0	1				1			
N1	2.13 (1.45- 3.11)	< 0.001			1.42 (0.75- 2.69)	0.587		
N2	3.06 (2.13- 4.40)	< 0.001			1.57 (0.92- 2.68)	0.184		
N3	1.73 (0.24- 12.49)	0.503			2.89 (1.65- 5.05)	< 0.001		
LNR								
LNR = 0	1		1		1		1	
0 < LNR < 0.4	2.26 (1.58- 3.23)	< 0.001	1.77 (1.07- 2.94)	0.027	1.62 (0.99- 2.66)	0.127	2.10 (1.10- 4.01)	0.025
LNR ≥ 0.4	3.11 (2.12- 4.56)	< 0.001	2.25 (1.32- 3.82)	0.003	3.03 (1.67- 5.50)	< 0.001	4.89 (2.40- 9.98)	< 0.001
pTNM stage								
I	1		1		1			
II	2.12 (1.27- 3.53)	0.030	2.04 (0.90- 4.56)	0.089	3.93 (1.48- 10.2)	0.034		

		3.52)		4.64)		10.45)			
III	3.34	(2.09-	0.001	2.15	(0.91-	0.080	5.45	(2.36-	0.049
		5.34)		5.08)		12.61)			
IVA	6.77	(3.67-	<	4.19	(1.64-	0.003	9.94	(4.03-	0.004
		12.51)	0.001	10.72)		24.51)			
Histopathology									
Adenocarcinoma	1						1		
Mucinous adenocarcinoma	1.52	(0.92-	0.051				1.89	(0.96-	0.051
		2.48)					3.72)		
Adeno-squamous carcinoma	1.53	(0.69-	0.228				1.04	(0.43-	0.931
		3.40)					2.51)		
Other types	0.99	(0.48-	0.993				-		-
		2.07)							
Differentiation									
High	1						-		-
Moderate	1.52	(0.92-	0.138				1		
		3.51)							
Poor	2.12	(1.29-	0.018				1.75	(1.19-	0.005
		3.50)					2.59)		
Bormann's type									
Type I	1						1		1
Type II	0.98	(0.58-	0.859				1.18	(0.62-	0.779
		1.66)					2.22)		2.13)
Type III	1.86	(1.11-	0.031				1.41	(0.80-	0.224
		3.14)					2.50)		3.13)
Type IV	1.35	(0.57-	0.711				6.79	(0.70-	0.001
		3.22)					65.62)		24.29)
Surgery procedure									
Subtotal esophagectomy with partial gastrectomy	1						1		
Total gastrectomy with partial esophagectomy	2.22	(0.84-	0.015				1.23	(0.67-	0.466
		5.85)					2.26)		
Chemoradiation									
No	1						1		1
Yes	0.81	(0.58-	0.227				0.70	(0.47-	0.070
		1.13)					1.03)		0.77)

CI, confidence interval, HR hazard risk, LNR lymph nodes ratio, NDLN number of dissected lymph nodes

Supplemental Legend

Fig. S1 The disease-specific survival was significantly different between the subgroup of number of dissected lymph nodes (NDLN) < 15 and NDLN ≥ 15.

Figures

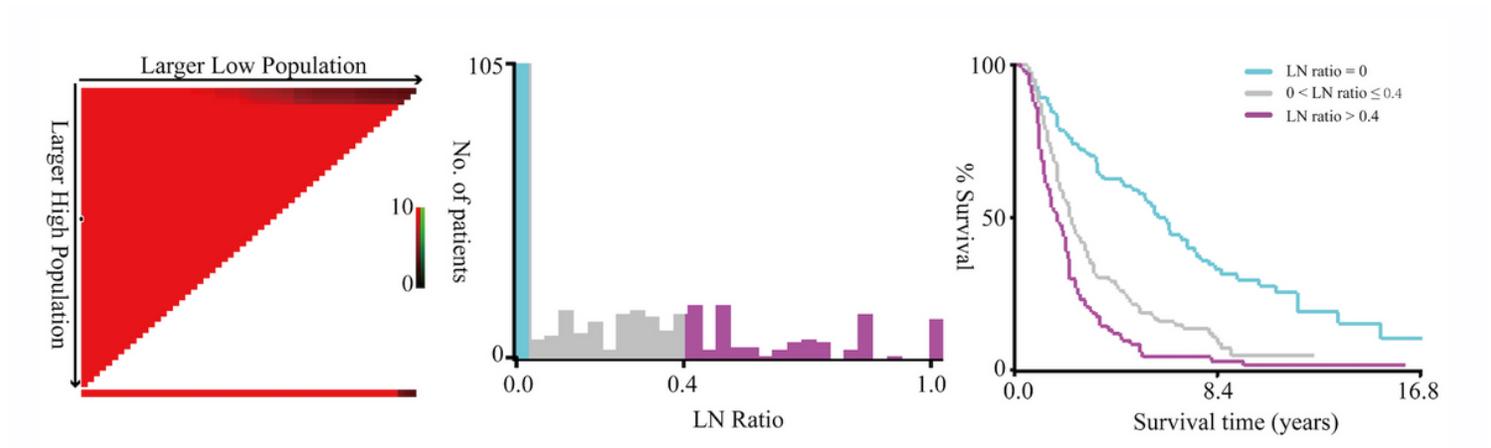


Figure 1

Optimal Cut-off values of lymph node ratio determined using X-tile software.

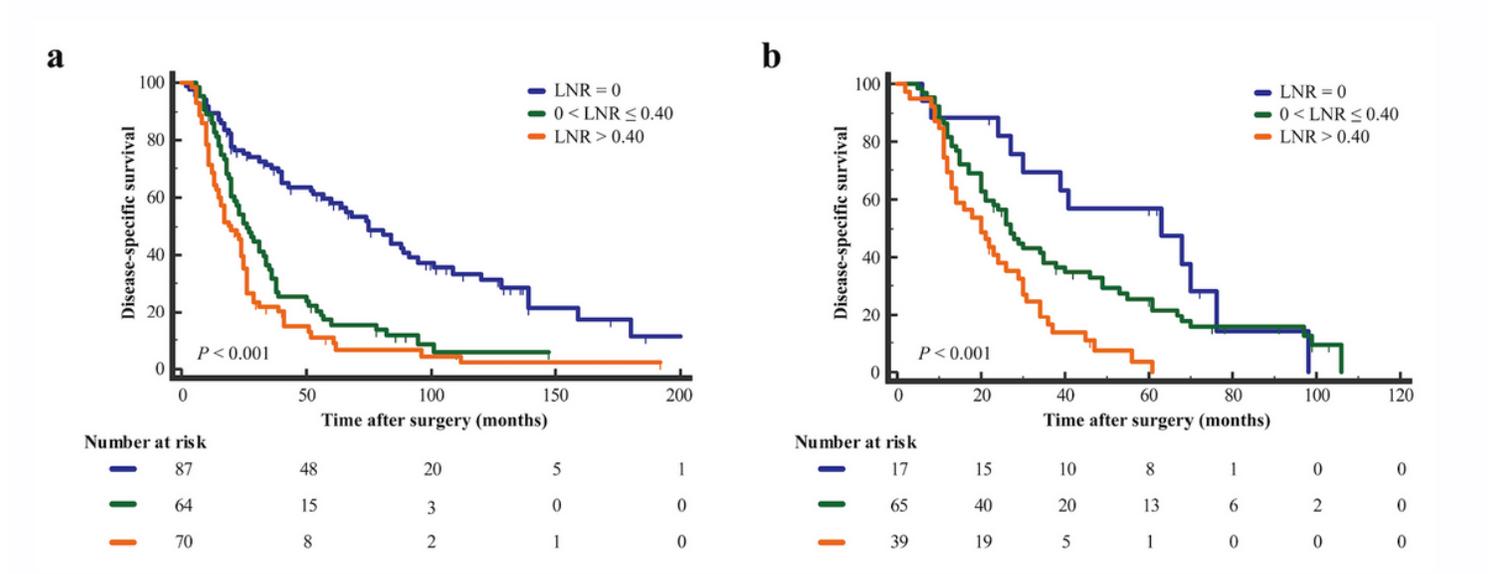


Figure 2

Kaplan–Meier survival analysis by number of dissected lymph nodes (NDLN). (a) There was significantly different of disease-specific survival (DSS) in the NDLN < 15 group; (b) There was significantly different of DSS in the NDLN ≥ 15 group.

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