Metastatic lymph node ratio and Lauren classification are independent prognostic markers for survival rates of patients with gastric cancer

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Abstract. The long-term prognosis for patients with gastric cancer (GC) following radical resection remains poor. It is important to identify prognostic markers to predict survival. In the present retrospective study, the association between the metastatic lymph node ratio (rN) and the Lauren classification on predicting overall survival (OS) was investigated. Furthermore, a subgroup analysis was performed on the Lauren classification, using rN score as an independent prognostic marker. In total, 261 pathologically confirmed patients with GC were retrospectively reviewed. Kaplan-Meier curves and Cox's proportional hazards modeling were applied to analyze the OS of patients, and were utilized in the subgroup analysis. Receiver operating characteristic (ROC) curves were used to compare the accuracy of prognosis between the rN score and lymph node staging (N stage). The χ^2 test was used to analyze the association between the rN score and Lauren classification. Univariate survival and multivariate analysis demonstrated that the rN score and Lauren classification were significant prognostic markers for patients with GC. The ROC analysis confirmed that the rN score was more effective than N staging for OS prediction. Subgroup analysis indicated that rN was more accurate at predicting OS time in patients with diffuse type GC. The rN score and the Lauren classification were independent prognostic factors for the OS of patients with GC following radical resection, and the rN score was more accurate than the N stage for predicting the prognosis. Overall, the rN may be suitable as an independent predictor for OS in patients with diffuse type GC.

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Introduction

Gastric cancer (GC) is the fourth most common type of cancer, and the second leading cause of cancer-associated mortality worldwide (1). GC mortality rates continue to increase yearly, particularly in low- and middle-income countries (2). The long-term prognosis remains poor due to postoperative recurrence and metastasis; and therefore, it is important to identify new prognostic markers for the identification of higher risk patients, and to direct the application of adjuvant chemotherapy regimens.

Several factors have been previously associated with the prognosis of patients with GC including tumor diameter, histological differentiation, lymph node status and surgical margin status. However, it has been demonstrated that the number of metastatic lymph nodes may be one of the most reliable prognostic markers available (3). At present, the 7th edition of the Tumor-Node-Metastasis (TNM) staging system by the American Joint Committee on Cancer (AJCC) (4) is commonly used to determine the stage of GC and its prognosis. N stage is determined by the number of metastatic lymph nodes. According to this classification, it is necessary to examine sufficient lymph nodes, with ≥15 required for the accurate diagnosis of the N stage in GC (4). However, an insufficient number of lymph nodes commonly hampers the clinical application of lymph node staging in GC specimens (5,6). Previously, the lymph node ratio (rN), defined as the ratio of metastatic lymph nodes to the total lymph nodes examined, has been demonstrated as a valuable prognostic factor for the overall survival (OS) of resectable GC (7-10). rN has been demonstrated as more reliable and accurate than N stage in predicting survival outcomes (11-13); however, another study has contradicted these studies (14). Further investigation is therefore required in order to resolve this conflict.

The Lauren classification sub-classifies GC into diffuse, intestinal and mixed type, with each type demonstrating distinct clinical and pathological characteristics (15,16). It has been demonstrated that diffuse type gastric carcinomas are associated with a worse prognosis than intestinal type gastric carcinoma, and that the Lauren classification type exhibits

independent prognostic significance (17). However, to the best of our knowledge, there has been no study analyzing the association between Lauren classification and rN on predicting the OS time for patients with GC.

The aims of the present study were to: i) Evaluate the prognostic value of the rN and Lauren classification in patients with GC; ii) compare the accuracy of prognosis between the rN and N stages in patients with GC; iii) investigate the prognostic relevance of the rN in each Lauren classification subtype.

Materials and methods

Eligible patients. For this retrospective study, the medical records for 332 patients who underwent curative GC resection between May 2007 and May 2011 at the Affiliated Hospital of Qing Dao University were reviewed and analyzed.

The inclusion criteria included: i) Pathologically confirmed adenocarcinoma; ii) the absence of distant metastasis at the time of primary diagnosis; iii) complete preoperative staging data was available; iv) the patient received radical tumor resection (R0) with D1 or D2 lymph adenectomy; v) complete postoperative pathological data was available.

The exclusion criteria included: i) Patients presented with multiple primary cancers; ii) patients received preoperative treatment; iii) patients had peritoneal dissemination during surgery; iv) patient mortality was caused by factors other than GC.

In total, 261 eligible patients were included in the present study (Fig. 1). Pathological lymph node status and Lauren classification were evaluated by pathologists, and the rN was calculated for each patient.

Clinical and pathological data collection and variable classification. Information on clinical and pathological variables were obtained from medical records and pathological reports, which included age, sex, smoking status, drinking status, tumor diameter, differentiation, pathological type, venous invasion, Lauren classification, node status, the number of lymph nodes examined, number of metastatic lymph nodes, T stage, N stage and the TNM stage evaluated according to the 7th edition of AJCC TNM staging system (18). Classification thresholds for tumor diameter (≤4, 4-6, 6-8, >8 cm) were defined by comparing survival rates between different sized groups using 1 cm as the standard interval, and the prognostic accuracy of all tumor diameter categories were evaluated based on the Harrell concordance index (19-24). The independent Ethics Committee of The Affiliated Hospital of Qingdao University (Shandong, China) approved the study.

According to the number of lymph nodes examined, patients were divided into two groups, ≥15 and <15 lymph nodes examined. rN was defined as the number of metastatic lymph nodes divided by the total number of lymph nodes examined. According to previous studies, rNs were divided into four score categories: i) rN0 (no lymph nodes involved); ii) rN1 (ratio >0 and ≤0.2); iii) rN2 (ratio >0.2 and ≤0.5); iv) rN3 (ratio >0.5) (25,26).

Follow-up. During the first 2 years after radical resection, patients were followed up via telephone contact at 3-month intervals. Between 2 and 5 years, follow-up was performed at 6-month intervals. After 5 years, patients were followed up once a year. In total, 16 patients lost to follow-up within the first year after surgery. In total, the follow-up period was between August 2007 and May 2016. The endpoint was the OS time, which was the time between the date of surgery and the date of final follow-up or patient mortality.

Table I. The characteristics of 261 patients with gastric cancer.

Variable	n	%
Sex		
Male	188	72.03
Female	73	27.97
Age, years		
<60	181	69.35
≥60	80	30.65
Tumor pathological differentiation		
Well	4	1.53
Moderate	43	16.48
Poorly	213	81.61
Unknown	1	0.38
Pathologic type		
Adenocarcinoma	245	93.87
Ring cell carcinoma	16	6.13
Tumor-node-metastasis stage		
I	25	9.58
II	118	45.21
III	118	45.21
Lymph nodes examined, n		
≥15	155	59.39
<15	106	40.61
Lymph node stage		
0	61	23.37
1	70	26.82
2	65	24.9
3	65	24.9
Metastatic lymph node ratio score		
0	61	23.37
1	81	31.03
2	71	27.20
3	48	18.39
Lauren classification		
Intestinal type	67	25.67
Diffuse type	77	29.5
Mixed type	117	44.83
Status		
Surviving	103	39.46
Deceased	158	60.54

TNM, tumor-node-metastasis.

Statistical analysis. Patient characteristics were evaluated using a Student's t-test for continuous data and a χ^2 test for categorical variables. Univariate analysis of survival was

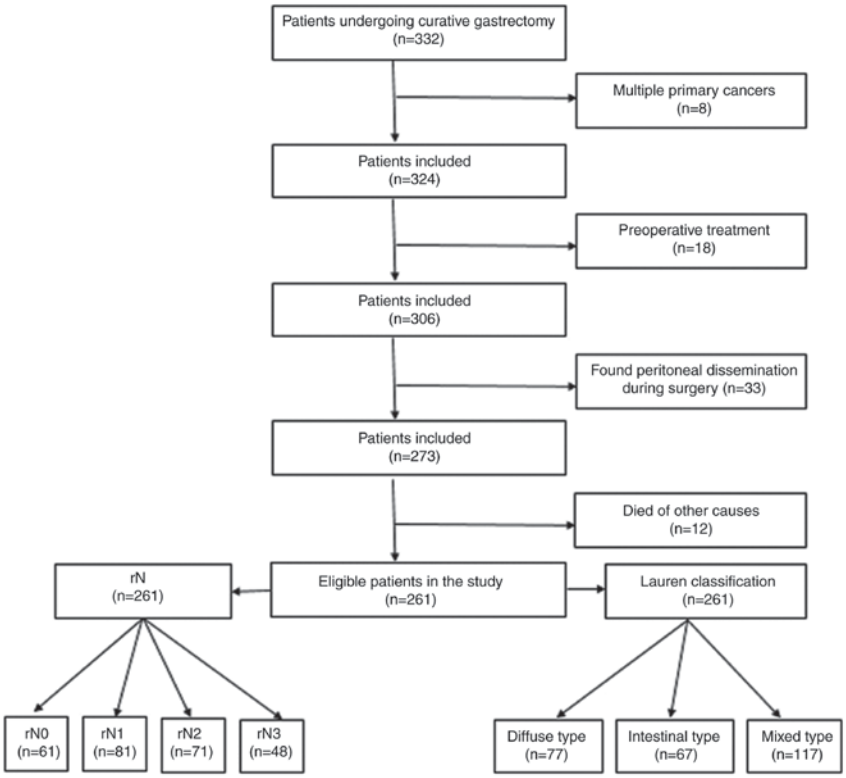

Figure 1. Flowchart of eligible patients enrolled in this study. rN, lymph node ratio.

performed using Kaplan-Meier estimator curves. The differences between groups were compared using the Log-rank χ^2 test. Multivariate analysis was performed using Cox proportional hazards modeling to identify independent predictors, which only included the variables with statistical significance (P<0.05) obtained from univariate analysis. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated in order to compare the relative risk associated with various factors. Receiver operating characteristic (ROC) curves were used to evaluate which variable demonstrated a higher prognostic value. Kaplan-Meier estimator curves for OS and Cox proportional hazard regression models were used to analyze the prognosis associated with the rN score in Lauren classification subgroups. The χ^2 test was applied to evaluate the association between the rN score and the Lauren classification. All statistical analysis was performed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. Patient characteristics are summarized in Table I. In total, 188 (72.03%) male and 73 (27.97%) female patients with a mean age of 54 years, primarily presenting with stage II and III disease (n=118, 45.21%), were enrolled in to the present study. Histopathological examination revealed that the majority of patients (n=213, 81.61%) were diagnosed with poorly differentiated adenocarcinoma, and 106 patients (40.61%) had <15 examined lymph nodes. The N-stage distribution was even among the 4 groups, whereas rN3 (n=48, 18.39%) was the least common category. Mixed type carcinoma (n=117, 44.83%) was the most common Lauren classification. In total, 103 patients (40.61%) survived and 158 patients (60.54%) had succumbed to GC by the end of the study. Overall, the median survival time was 30 months (range, 3-63 months).

Analysis of prognostic factors in the whole patient cohort. As presented in Table II, the univariate survival analysis with Kaplan-Meier curves demonstrated that the significant prognostic factors for OS included tumor diameter (P<0.001), node status (P=0.004), rN score (P=0.001), Lauren classification (P<0.001), N stage (P=0.001) and TNM stage (P<0.001), whereas sex (P=0.486), age (P=0.169), T stage (P=0.104), pathological differentiation (P=0.43), the number of lymph nodes examined (P=0.813), vessel cancer embolus (P=0.675), smoking status (P=0.843), drinking status (P=0.85) and pathological type (P=0.189) were not significantly associated with OS (Fig. 2).

As presented in Table III, multivariate analysis with Cox regression model further identified the independent prognostic factors for OS, including tumor diameter (P=0.03), rN score (P<0.001) and Lauren classification (P<0.001). Multivariate analysis also indicated that patients with an increased rN were associated with the shortest OS time, and the diffuse type of Lauren classification was also associated with a poorer prognosis. In the analysis of rN score, using rN3 as the reference group, the HRs for rN0, rN1, and rN2 were 0.16 (95% CI, 0.14-0.19), 0.22 (95% CI, 0.2-0.25) and 0.3 (95% CI, 0.28-0.31), respectively. In Lauren classification analysis, using mixed type as the reference group (HR: 1), the HRs for intestinal and diffuse type were 0.56 (95% CI, 0.32-0.97) and 1.9 (95% CI, 1.26-2.86), respectively.

Table II. Univariate analysis of the potential predictive factors for overall survival time.

Variable	Median	Standard error	95% confidence interval	χ^2	P-value
Sex					
Male	74.73	3.01	68.83-80.63	0.485	0.486
Female	70.36	5.27	60.03-80.69		
Age, years					
<60	76.14	3.11	70.03-82.24	1.891	0.169
≥60	67.59	4.85	58.09-77.09		
Tumor diameter, cm					
≤4	86.31	3.93	78.6-94.01	19.276	<0.001
4-6	72.44	4.41	63.8-81.07		
6-8	53.03	6.22	40.83-65.23		
>8	65.07	7.71	49.96-80.17		
T stage					
1	93.33	10.06	73.62-113.04	6.166	0.104
2	85.38	6.29	73.06-97.7		
3	74.71	3.59	67.67-81.76		
4	48.92	4.06	40.96-56.88		
Differentiation					
Well	39.75	10.14	19.88-59.62	2.759	0.430
Moderate	72.58	6.42	59.99-85.18		
Poor	75	3.03	69.07-80.94		
Unknown	52	0	52.00-52.00		
Pathological type					
Adenocarcinoma	75.97	2.77	70.54-81.41	1.728	0.189
Ring cell carcinoma	55.85	11.3	33.71-77.99		
Node status					
Negative	88.33	4.32	79.86-96.81	8.398	0.004
Positive	69.27	3.11	63.18-75.36		
Lymph nodes examined, n					
≥15	73.72	3.35	67.14-80.29	0.056	0.813
<15	73.03	4.2	64.79-81.27		
N stage					
0	88.33	4.32	79.86-96.81	15.804	0.001
1	74.7	5	64.9-84.5		
2	73.77	5.17	63.63-83.9		
3	57.9	5.5	47.12-68.69		
Metastatic lymph node ratio score					
0	87.52	2.72	82.19-92.85	19.407	0.001
1	76.28	2.57	71.24-81.32		
2	65.91	2.56	60.89-70.93		
3	54.29	3.08	48.25-60.33		
TNM stage					
I	88.13	6.91	74.6-101.66	20.616	<0.001
II	83.95	3.51	77.07-90.82		
III	59.61	4.16	51.46-67.75		
Lauren classification					
Intestinal type	89.07	2.79	83.60-94.54	23.746	<0.001
Diffuse type	54.65	4.97	44.91-64.39		
Mixed type	74.85	3.65	67.70-82.00		

Table II. Continued.

Variable	Median	Standard error	95% confidence interval	χ^2	P-value
Vessel cancer embolus					
Negative	74.1	2.69	68.83-79.37	0.176	0.675
Positive	58.78	12.85	33.6-83.96		
Smoking status					
No	73.98	3.34	67.43-80.53	0.039	0.843
Yes	72.34	4.26	63.98-80.69		
Drinking status					
No	73.33	3.31	66.83-79.82	0.036	0.85
Yes	73.68	4.32	65.21-82.15		

TNM, tumor-node-metastasis; N stage, lymph node staging; T stage, tumor stage.

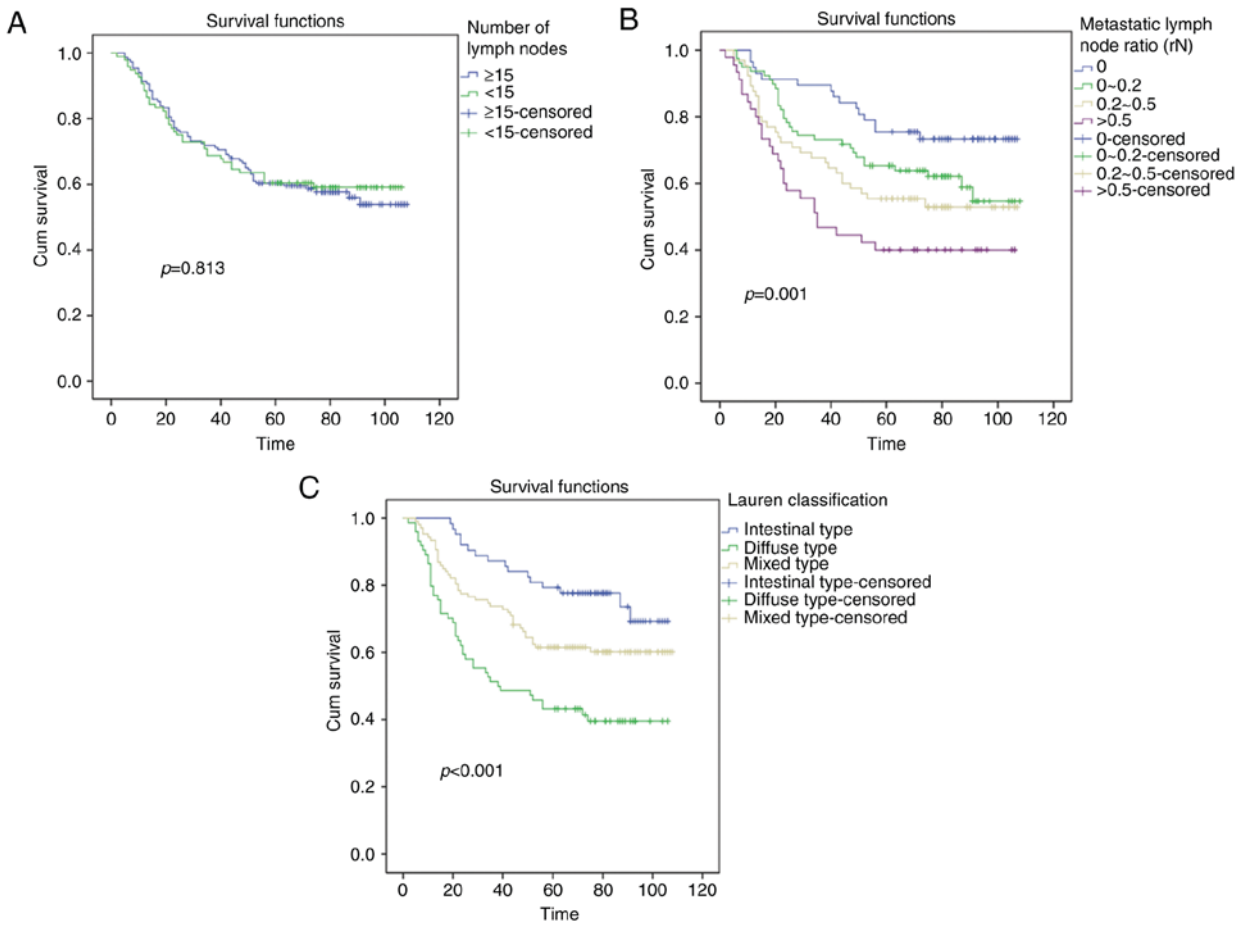

Figure 2. Kaplan Meier curve of overall survival. (A) Overall survival curves of patients according to the number of lymph nodes examined. (B) Overall survival curves of patients according to (C) Overall survival curves of patients according to Lauren classification. rN, lymph node ratio.

As demonstrated in ROC curves from multivariate analysis, the area under the curve for rN and N stage was 0.765 (95% CI, 0.704-0.827) and 0.614 (95% CI, 0.544-0.683), respectively, a statistically significant difference (P=0.002). The rN score had a greater prognostic value for OS compared with N stage (Fig. 3). In the ROC curve analysis, N stage and the rN score were used as test variables, and the survival status of patients was used as the outcome variable; these variables were incorporated into a model and a correction curve was generated.

Subgroup analysis for OS. Kaplan-Meier estimator curves were used to analyze whether the number of lymph nodes examined (≥15 or <15) had an effect on the prognostic value of rN. An association analysis was performed separately for the two groups and demonstrated that rN was significantly

Table III. Multivariable Cox regression analysis to identify independent predictors of overall survival time.

Variable	HR	% confidence 95 interval	P-value
Tumor diameter			0.030
1	0.72	0.27-1.95	0.520
2	0.78	0.34-1.81	0.560
3	2.44	1.24-4.93	0.023
4	1		
Lymph node metastasis	1.42	0.45-4.49	0.550
rN score			<0.001
0	0.16	0.14-0.19	<0.001
1	0.22	0.20-0.25	<0.001
2	0.3	0.28-0.31	<0.001
3	1		
Lauren classification			<0.001
Intestinal type	0.56	0.32-0.97	0.043
Diffuse type	1.9	1.26-2.86	0.003
Mixed type	1		
N stage			0.270
N0	2.36	0.57-9.88	0.310
N1	1.9	0.83-4.32	0.250
N2	0.67	0.32-1.40	0.290
N3	1		
TNM stage			0.390
I	0.34	0.06-1.87	0.210
II	0.61	0.25-1.49	0.280
III	1		

N stage, lymph node stage; rN, metastatic lymph node ratio; TNM, tumor-node-metastasis.

Table IV. Survival rates stratified by rN score.

	Survival rate, %		
rN score	1-year	3-year	5-year
0	91.23	84.21	75.44
1	79.49	70.49	63.71
2	72.31	58.46	55.34
3	60.00	44.44	39.89

rN, metastatic lymph node ratio.

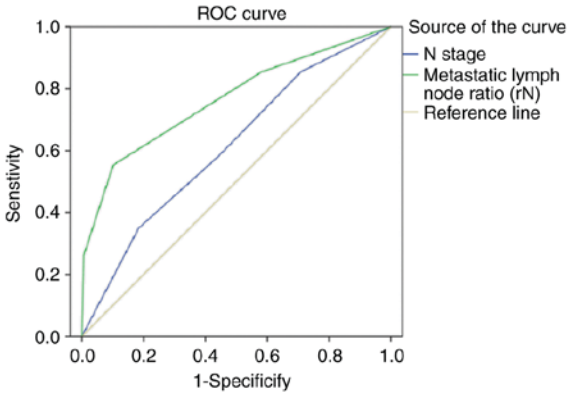

Figure 3. Receiver operating characteristic curve to compare the accuracy of prognosis between rN and N stage by the area under the curve on overall survival of patients underwent curative surgery for gastric cancer. rN, lymph node ratio.

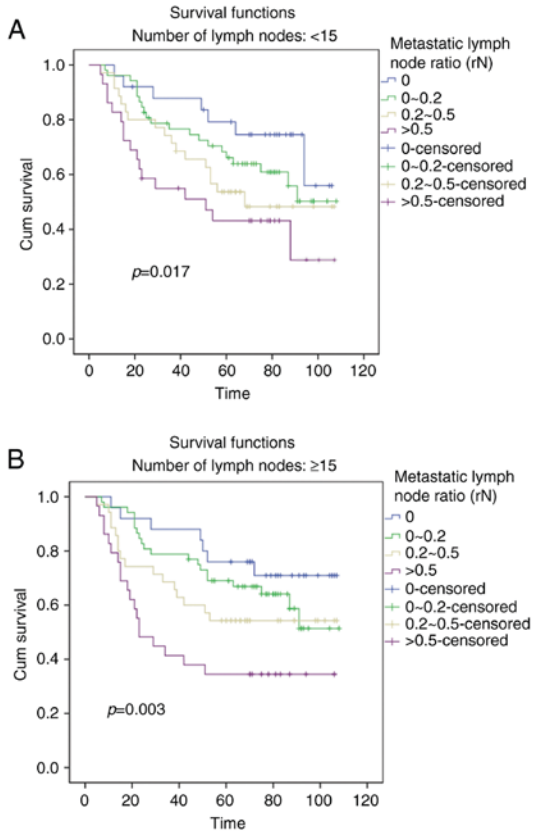

Figure 4. Kaplan-Meier survival curves of rN. (A) Overall survival curves of rN in a group of the number of lymph nodes examined fewer than 15 (B) Overall survival curves of rN in the other group of the number of lymph nodes examined more than 15. rN, lymph node ratio.

associated with OS in both groups (P=0.003 and P=0.017, respectively). The results confirmed that the rN score was an independent prognostic factor for survival rate, independent of the number of lymph nodes examined (Fig. 4). The survival rates associated with different rN scores were calculated at 1, 3 and 5 years. The results demonstrated that increased rN was associated with shorter OS (Table IV).

The association between rN scores and the Lauren classification for OS was evaluated using subgroup analyses. Kaplan-Meier curves and Cox's proportional hazard regression models were used to analyze the prognostic relevance of the rN score categories in each Lauren classification (diffuse, intestinal and mixed type). A significant association with survival was only observed in the diffuse type subgroup (P=0.01; Fig. 5 and Table V). The χ^2 test was applied to evaluate the association between the rN score and the diffuse type subgroup. No

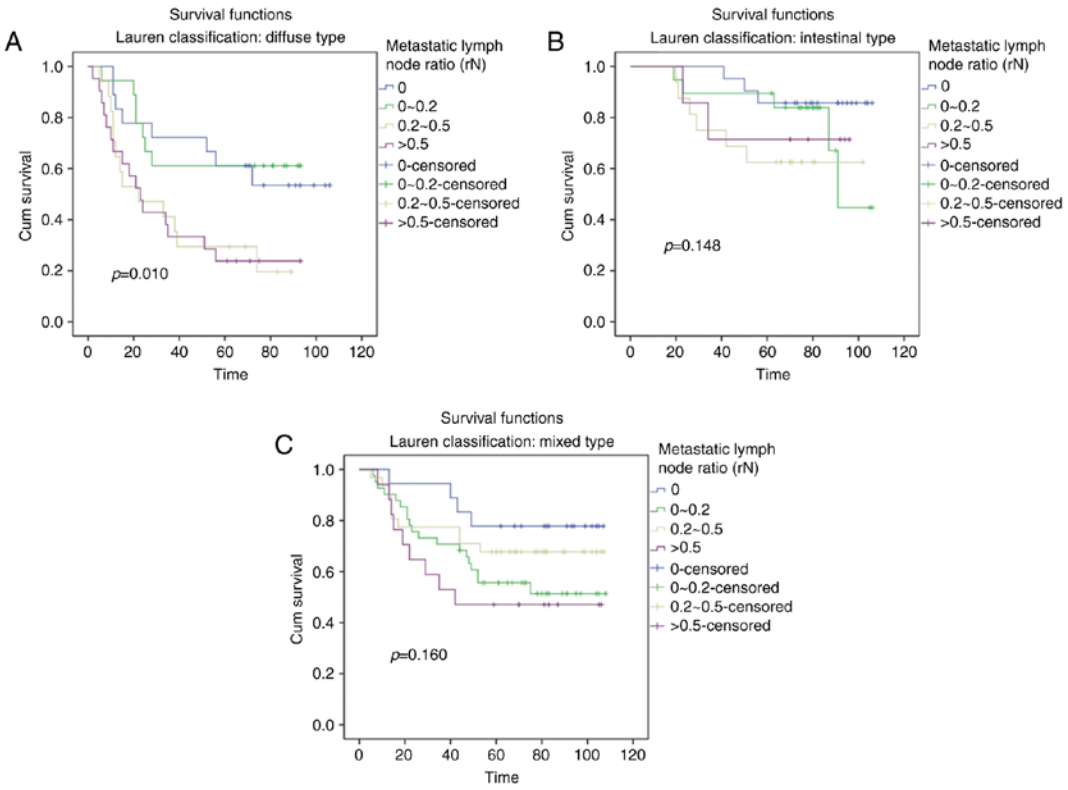

Figure 5. Kaplan-Meier survival curve analysis of the prognostic relevance of rN categories in each Lauren classification. (A) Overall survival of rN in the diffuse-type. (B) Overall survival of rN in intestinal-type. (C) Overall survival of rN in mixed-type. rN, lymph node ratio.

association was identified between the two factors (P=0.223; Table VI), implying that the rN score may be used as an independent prognostic factor for OS in the diffuse type subgroup. Cox regression model analysis in the diffuse type subgroup further confirmed this (Table VII). In the diffuse type subgroup, univariate analysis with Kaplan-Meier estimator curves were used to select significant factors, including the rN score (P=0.01), N stage (P=0.032) and TNM stage (P=0.004). Multivariate analysis with Cox regression model demonstrated that the rN score was an independent predictor for OS time (P<0.001).

Discussion

The present study demonstrated that the score and Lauren classification had independent prognostic relevance on predicting the survival of postoperative patients with GC. Overall, the rN score demonstrated a better prognostic value compared with the N stage, and an increased rN score was associated with a shorter OS time.

The N stage is based on the number of local lymph nodes exhibiting metastasis, and has been used in routine clinical practice for years, as it possesses significant diagnostic value for patients with GC. However, it has been demonstrated that an insufficient or extended number of lymph nodes being examined may cause staging deviation (4), which is observed in ~15% of patients with GC when using the TNM staging system (27). rN therefore is associated with potential advantages in minimizing the stage migration phenomenon for patients with an insufficient number of assessed lymph nodes. Using rN alongside the TNM system may assist in predicting the relapse and survival rates for patients with GC. However, another study could not confirm this result and reported no benefit of rN over N stage in the prediction of patient outcome (28). In the present study, ROC curves were used to compare the prediction accuracy between rN and N stage. The results demonstrated that rN was a better metric than N stage for predicting the patient outcome. However, as the sample size was small, future investigations with a larger cohort are required in order to validate these results.

According to the current TNM staging system, it is necessary to examine ≥15 lymph nodes. However, this is often not achievable in practice due to a surgeon's lack of experience and the low extent of surgical lymph node dissection. This may lead to stage underestimation and affect the management and/or prognosis of a patient. Previous studies have suggested that rN may still accurately predict patient prognosis, despite requiring an examination of <15 lymph nodes (10,26). The present study is in accord with these results. In Western countries, extended lymph node dissection is not considered to provide survival benefit for patients; D1 radical resection is frequently performed, leading to <15 lymph nodes being examined (29,30). The results from the present study suggested that the number of examined lymph nodes did not exhibit significant prognostic value for OS.

A number of studies have focused on the prognostic significance of rN in other types of malignant tumor, including esophageal carcinoma (31), breast cancer (32), non-small cell lung cancer (33), colon cancer (34), pancreatic adenocarcinoma (35) and carcinoid tumors (36). The rN was identified to be an independent prognostic marker in these types of tumor, with the exception of carcinoid tumors (36). Consistent with these results, the present study demonstrated that the rN score was a significant prognostic factor based on univariate and

Table V. Cox's proportional hazard regression models to analyze the prognosis associated with rN score for each Lauren classification type.

Lauren classification	rN score	Median	Hazard ratio	95% confidence interval	P-value
Intestinal type	0	92.89	0.81	0.640-1.025	0.080
	1	86.34	0.85	0.713-1.014	0.070
	2	78.61	0.87	0.715-1.058	0.164
	3	70.88	1	-	-
Diffuse type	0	72.06	0.67	0.573-0.784	<0.001
	1	70.38	0.71	0.595-0.847	<0.001
	2	40.62	0.97	0.862-1.091	0.665
	3	36.41	1	-	-
Mixed type	0	87.42	0.84	0.677-1.042	0.113
	1	76.43	0.91	0.778-1.064	0.238
	2	67.08	0.93	0.811-1.067	0.299
	3	60.23	1	-	-

HR, hazard ratio; CI, confidence interval; rN, metastatic lymph node ratio.

Table VI. χ^2 test analysis of the association between rN score and Lauren classification.

Lauren classification	rN score				χ^2	P-value
	0	1	2	3		
Intestinal type	21	19	18	8	8.217	0.223
Diffuse type	19	19	17	22		
Mixed type	21	43	35	18		

rN, metastatic lymph node ratio.

Table VII. Cox regression analysis to identify independent prognostic predictors of survival in the diffuse type subgroup.

Variable	Hazard ratio	95% confidence interval	P-value
Lymph node stage			0.163
1	0.90	0.77-1.05	0.187
2	1.21	0.92-1.59	0.173
3	0.77	0.59-1.01	0.054
4	1		
Tumor-node-metastasis stage			0.281
I	0.78	0.58-1.04	0.100
II	0.70	0.41-1.18	0.191
III	1		
Metastatic lymph node ratio score			<0.001
0	0.58	0.49-0.70	<0.001
1	0.63	0.48-0.81	<0.001
2	0.95	0.85-1.07	0.366
3	1		

multivariate analyses, as an increased rN score was associated with a reduced OS time.

Lauren classification is the most commonly used histological system for GC, dating back to 1965. Each classification type has distinct pathological, epidemiological and prognostic characteristics. Previous studies have reported the relevance of the Lauren classification, especially the diffuse and intestinal type, in regards to survival prediction (16,17,37). Qiu *et al* (38) demonstrated that Lauren classification was an independent prognostic factor, as the patients with diffuse type GC had a worse prognosis compared with the patients with intestinal type GC (38). However, Berlth *et al* (39) indicated that the Lauren classification was not associated with patient OS. The study did not identify that the diffuse type was independently associated with a poor prognosis, and the Lauren classification was only associated significantly with prognosis in univariate analysis and not in multivariate analysis (39). In the present study, Lauren classification was identified as an independent prognostic factor for OS in univariate and multivariate analysis. The diffuse type classification was associated with the worst prognosis, consistent with the results presented by Qiu *et al* (38). The present study also conducted subgroup analysis based on the Lauren classification. The association of the rN score with the prognosis in each subgroup was assessed. The rN score was identified as an independent predictor of survival in the diffuse type subgroup. The χ^2 test was applied to assess whether the rN score and the Lauren classification influenced one another; it was demonstrated that there was no association between the rN score and the diffuse type subgroup. Therefore, rN may be suitable as an independent prognostic marker for patients with diffuse type GC. Cox

regression modal analysis of the diffuse type subgroup further supported this conclusion. To the best of our knowledge, this is the first report to demonstrate that rN exhibited particular prognostic significance for patients with diffuse type GC.

The results of the present study should be considered in the context of its limitations. The sample size of the present study was not large enough for analysis by further subgroup stratification. Therefore, future studies with larger sample sizes are required in order to validate the results obtained from subgroup analysis. Additionally, univariate analysis demonstrated that tumor diameter was a significant predictor of GC whereas the T stage was not. This may have been due to stage distribution bias in the cohort of the present study. The use of a larger sample size may allow the production of more consistent results.

In conclusion, the present study demonstrated that the rN score and the Lauren classification were independent prognostic factors for the OS for patients with GC following radical resection. It was determined that the rN score was more effective at predicting OS for patients with GC following radical resection than N staging. The data also demonstrated that rN may be used as an independent predictor of survival in patients with diffuse type GC.

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