Cohort Study

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Evaluation of the prognostic value of negative to positive lymph node ratio in gastric cancer: results from multi-institutional cohorts from western and eastern datasets – Cohort study

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Introduction: Lymph node (LN) stage is important for prognosis evaluation of gastric cancer (GC) patients. This study aimed to evaluate the prognostic value of the ratio of negative to positive LNs (Rnp) in GC.

Methods: The authors evaluated the clinical significance of the Rnp stage in 7660 GC patients from three high-volume institutions in China. Meanwhile, the authors verified the value of the Rnp stage in 11 234 GC patients from the Surveillance, Epidemiology, and End Results (SEER) database.

Results: The patients were stratified into different subgroups based on the N stage of the eighth edition of the TNM staging system, the ratio of positive to detected LNs (Rpd) and Rnp. The survival analysis showed clear differences between the three LN stages in both the China and Surveillance, Epidemiology, and End Results cohorts. In univariate and multivariate analyses, the Rnp stage provided smaller Akaike information criterion or Bayesian information criterion values and a larger likelihood ratio χ^2 than the N or Rpd stages in both two cohorts. For patients with inadequate examined LNs (< 16), the Rnp stage showed better prognostic evaluation performance than the other two stages. In addition, the 5-year disease-specific survival of GC patients showed a slight variation with increasing LNs in the same subgroup classified by the Rnp or Rpd stages compared to the N stage.

Conclusions: Along with the higher prognostic value, the Rnp stage has excellent universality with GC patients compared to the N or Rpd stages. Studies with larger sample sizes are needed to predict the prognosis and provide more precise treatment for GC patients.

Keywords: gastric cancer, lymph node stage, prognosis, SEER

Introduction

The *American Joint Committee on Cancer (AJCC)* and the *Union for International Cancer Control (UICC)* gastric cancer (GC) TNM staging system is developed based on the depth of tumor invasion, lymph node metastasis, and distant metastasis. The TNM staging system has been modified several times and has played an important role in prognosis evaluation and making clinical decisions of GC patients[1–4]. In the current edition of the TNM staging system, the N stage is classified based on the number of positive lymph nodes (pLNs). However, a growing number of studies found that patients were prone to induce staging migration due to the insufficient number of examined lymph nodes (eLNs).

Previous studies demonstrated that the ratio of positive lymph nodes to dissected LNs (Rpd), which represented the density of LNs metastases[5,6], could reduce the occurrence of staging migration[2,3,7–10]. Our previous study also found that TNM stage combined with Rpd stage had a better prognosis evaluation than TNM stage alone[3]. Nevertheless, the Rpd stage ignores the prognosis value of negative LNs (nLNs) in prognosis evaluation. Actually, patients with the N0 stage may also occur local recurrence or distant metastases after radical surgery. This indicated

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the possible existence of isolated tumor cells or negative LN micrometastases in N0 stage patients [3]. Several studies demonstrated that appropriate dissection of nLNs was conducive to clearing micrometastases that are hard to be diagnosed by pathology[3,11]. Hence, more studies proposed the ratio of negative to positive LNs (Rnp), which was an independent prognostic predictor of GC patients and could evaluate the prognosis more accurately than TNM staging[9,11,12].

Our previous studies indicated that Rnp stage had a superior prognostic predictive value in GC patients in China and Japan cohorts[12]. Nonetheless, this evaluation system may not be applicable to other GC patients due to different criteria for the number of LNs detected between Western countries and Asian countries. Therefore, it is imperative to explore a more complete prognostic system based on the TNM staging, which could be applied to more GC patients. Our study aimed to establish and compare the prognostic prediction model of Rpd and Rnp based on TNM staging using patients from three high-volume centers in China and verified by the Surveillance, Epidemiology, and End Results (SEER) dataset.

HIGHLIGHTS

- The ratio of negative to positive LNs (Rnp) stage has higher prognostic value and better universality with the gastric cancer patients compared to the N or ratio of positive to detected LNs stages.
- The Rnp stage showed good prognostic evaluation performance even in the case of inadequate examined lymph nodes.
- The 5-year disease-specific survival of gastric cancer patients showed a slight variation with increasing lymph nodes in the same subgroup classified by the Rnp stage.

Methods

Patient source

With the approval of the Institutional Ethics Committee at each participating institution and the *Research Registry* (www.researchregistry.com), patients who underwent curative surgery at three high-volume centers in China, from January 2000 to December 2012, were selected into a prospectively maintained database.

Patients histologically diagnosed as having gastric adenocarcinoma were included. Patients who received preoperative neoadjuvant chemotherapy and/or radiotherapy were excluded. Patients with missing examined LNs were not evaluated. We also excluded patients who died during the perioperative period (within 30 days) or loss of follow-up. For patients whose tumor site was cardia or esophagogastric junctional were further identified as our previously study described[13]. Patients with tumor location classified as esophageal cancer according to the eighth

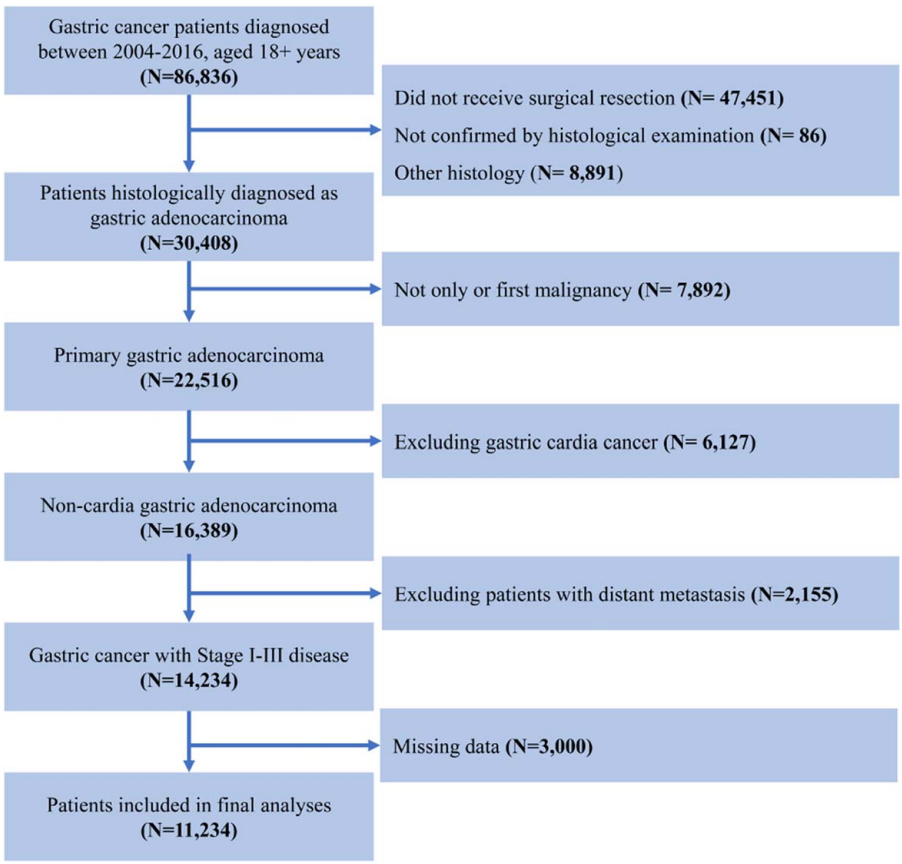

Figure 1. Flowchart for selection of the Surveillance, Epidemiology, and End Results (SEER) patient dataset.

edition of the AJCC Cancer Staging Manual were also excluded[14]. The included patients with preoperative clinical TNM stage as cT1aN0M0 underwent D1 lymphadenectomy, those with stage as cT1bN0M0 underwent D1+ lymphadenectomy, and those with stage as cT1N+M0 or cT2-4NxM0 underwent D2 lymphadenectomy in accordance with the *Japanese Classification of Gastric Carcinoma*, and were confirmed to have R0 resection after surgery. Finally, 7660 patients were included in further analysis.

The validation cohort was from the SEER-18 program of the National Cancer Institute. Patients aged 18+ years old and diagnosed as GC during 2004–2016 were eligible. Patients were included with the following characteristics: underwent surgical resection and histologically diagnosed as gastric adenocarcinoma, single primary malignant, noncardia tumor, TNM stage I–III, complete clinicopathological information. The stepwise extraction process was presented in Figure 1. And a total of 11 234 patients were included for analysis.

In both cohorts, we only collected the following demographic and pathologic characteristics: sex, age, tumor location, the depth of tumor invasion, the number of eLNs and metastasis LNs (mLNs), the survival time, and the survival status. The T stage and N stage were classified according to the eighth edition of the AJCC Cancer Staging Manual[14].

Statistical analysis

The continues variables for the clinicopathological characteristics are presented as mean ± SD or as median with interquartile range. Categorical variables are described as counts and proportions. The follow-up time was evaluated using the reverse Kaplan–Meier method[15,16]. The disease-specific survival (DSS) was estimated using the Kaplan–Meier method and compared using the log-rank test. A multivariable Cox proportional hazards regression model was applied to identify the independent prognostic factors among those clinicopathological characteristics.

Patients with no LNs metastasis were classified into Rnp0 and Rpd0 stages. The other three optimal Rpd and Rnp intervals for patients with mLNs were determined by using the X-Tile software (X-Tile version 3.6.1 Yale University), which estimated the log-rank χ^2 value for each possible division of the continues variable[17]. Additionally, these cutoff values were also validated using the martingale residual analyses.

The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) values within a Cox proportional hazard regression analysis were used to evaluate the discriminatory ability of different LN stages. A smaller AIC or BIC value indicates a better model for prognosis evaluation[18,19]. Also, the likelihood ratio χ^2-test was used to assess the homogeneity of the given prognosis model[20].

The effect of the number of eLNs on survival for each LN staging was evaluated by estimating the 5-year DSS rate according to different eLNs group. The tendency of survival to change according to the number of eLNs was estimated using the linear regression test.

The analyses were performed using the R software version 3.2.1 (http://www.r-project.org/) and SPSS version 21.0 (SPSS). A two-tailed *P*-value less than 0.05 was considered statistically significant in all analyses.

The work has been reported in line with the strengthening the reporting of cohort studies in surgery (STROCSS) criteria[21].

Results

The basic demographic and pathological characteristics of two cohorts were presented in Table 1. Patients from these two cohorts had extremely different clinicopathological characteristics. Patients in the SEER cohort were older (58.28 vs. 66.49, $P<0.001$) and had more female patients (29.4 vs. 44.0%, $P<0.001$) than in the China cohort. The most common tumor sites in both cohorts were the antrum or pylorus. Patients from the SEER cohort had more pT1 patients than the China cohort, whereas almost half of patients were classified into pT4a stage in China cohort. For LN status, the China cohort had more advanced N stages and less patients with insufficient LNs retrieved (30.1 vs. 51.0%, $P<0.001$) than the SEER cohort. The 5-year DSS in China and SEER cohort were 54.6% (95% CI: 53.3–55.8%) and 52.2% (95% CI: 51.2–53.3%), respectively.

Based on the results of X-tile software using the China cohort dataset, novel LN ratio classification was established as follows: Rpd0 (0%), Rpd1 (1–25%), Rpd2 (25.1–50.0%), and Rpd3 (>50%). Additionally, we also established the novel Rnp stage using the same method and the classifications were as follows: Rnp0 (Negative lymph node), Rnp1 (> 4.13), Rnp2 (0.74–4.12),

Table 1

Basic demographic and clinical characteristics of patients included in the analysis.

Clinicopathological characteristics	China Cohort *n* = 7660 (%)	SEER Cohort *n* = 11234 (%)	*P*
Sex			< 0.001
Female	2255 (29.4)	4941 (44.0)	
Male	5405 (70.6)	6293 (56.0)	
Age (years)			< 0.001
< 60	4006 (52.3)	3340 (29.7)	
≥ 60	3654 (47.7)	7894 (70.3)	
Mean ± SD	58.28 ± 11.72	66.49 ± 13.71	< 0.001
Median (IQR)	59 (50–67)	68 (57–77)	
Tumor location			< 0.001
Antrum/Pylorus	3501 (45.7)	4684 (41.7)	
Body	1480 (19.3)	1424 (12.7)	
Fundus	2042 (26.7)	460 (4.1)	
Overlapping regions	637 (8.3)	1072 (9.5)	
Lesser/Greater curvature	–	2433 (21.7)	
Stomach NOS	–	1161 (10.3)	
pT stage			< 0.001
pT1	950 (12.4)	2713 (24.1)	
pT2	1412 (18.4)	1470 (13.1)	
pT3	1255 (16.4)	3733 (33.2)	
pT4a	3549 (46.3)	2476 (22.0)	
pT4b	494 (6.4)	842 (7.5)	
pN stage			< 0.001
pN0	2811 (36.7)	4772 (42.5)	
pN1	1372 (17.9)	1908 (17.0)	
pN2	1488 (19.4)	1889 (16.8)	
pN3a	1346 (17.6)	1847 (16.4)	
pN3b	643 (8.4)	818 (7.4)	
Examined lymph nodes			< 0.001
< 16	2303 (30.1)	5728 (51.0)	
≥16	5357 (69.9)	5506 (49.0)	
Mean ± SD	23.16 ± 13.09	17.88 ± 12.83	< 0.001
Median (IQR)	21 (14-30)	15 (9-24)	

IQR, interquartile range; NOS, not otherwise specified; SEER, the surveillance, epidemiology, and end results.

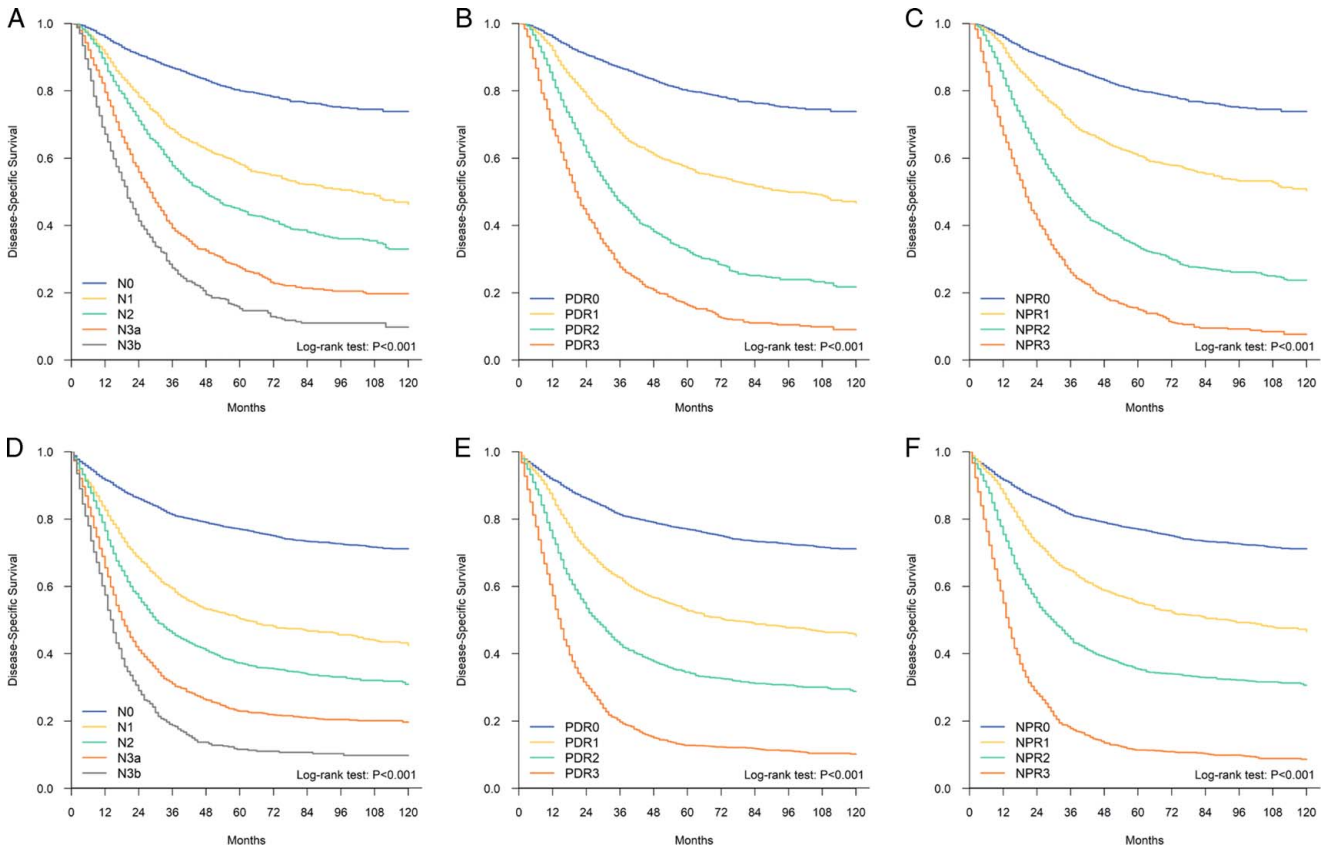

Figure 2. The survival curve of gastric cancer patients in China cohort classified by the N stage of the eighth edition TNM staging system (A), the Rpd staging system (B) and the Rnp staging system (C). The survival curve of gastric cancer patients in Surveillance, Epidemiology, and End Results cohort divided by the N stage of the eighth edition TNM staging system (D), the Rpd staging system (E) and the Rnp staging system (F). Rpd, the ratio of positive lymph nodes to detected lymph nodes; Rnp, the ratio of negative lymph nodes to positive lymph nodes.

Rnp3(< 0.74). The survival curves showed that the N stage, Rpd stage, and Rnp stage were all showed significant survival difference in the China cohort (Fig. 2a-c). We also validated these three stages in the SEER cohort and the same results were observed (Fig. 2d–f).

In univariate analyses, age, tumor location, AJCC T stage, AJCC N stage, Rpd stage, and Rnp stage were identified as significant prognostic factors in both cohorts. However, the survival benefit with more lymph nodes retrieved were only obtained in the China cohort, but not in the SEER cohort (Table 2).

In univariate analyses, the Rnp stage provided better discriminatory and homogeneity with smaller AIC or BIC values and a larger likelihood ratio χ^2 than the N stage and Rpd stage in both the China cohort and the SEER cohort. To explore the impact of other significant clinicopathological characteristics on the prognostic performance of LN stage, we performed multivariate analyses in both cohorts. After adjusting for the effect of other clinicopathological characteristics, the Rnp stage showed better discriminatory and homogeneity ability in the prognosis evaluation than the other two LN stages (Table 3).

We further identified the prognosis evaluation superiority of Rnp stage in different LN retrieved groups. For patients with inadequate LNs retrieved (< 16), Rnp stage showed better prognostic evaluation performance than the N stage and the Rpd stage in both cohorts. The same results could also be observed in patients with more than 16 LNs retrieved (Table 4).

To elucidate the survival impact of different eLNs in LNs metastasis patients, the 5-year DSS was estimated according to the number of eLNs in each stage. The survival changing trend in two cohorts showed that survival rates increased in a linear manner with 10 additional eLNs in AJCC N stages, especially for patients in N1–N3a stages. However, when we classified patients into Rpd and Rnp stages, the survival changes were minimal except for a slight increase in Rpd1 and Rnp1 patients (Figure. 3).

Discussion

The AJCC/Union for International Cancer Control TNM staging system is the most common used system for prognostic evaluation in malignant tumors. It comprehensively evaluates the progression of GC based on the tumor invasion, lymph node metastasis and distant metastasis, and provide reasonable therapy suggestions[1,22,23]. Among the TNM staging system, N stage is classified according to the number of mLNs. However, this classification only considers positive LNs, and staging migration is occurred in about 5–15% of patients[24-26]. Stage migration is closely related to tumor progression, the extent of lymph node dissection, patients' own conditions (such as the patient's visceral fat, autoimmune capacity), and other factors[27–29]. Therefore, many researchers proposed new prognostic indicators to eliminate the stage migration effect on GC patients.

Table 2

Five-year disease-specific survival rates of patients from two cohorts.

	China Cohort ($n=7660$)			SEER Cohort ($n=11234$)		
Characteristics	**Number**	**5-YDSS**	***P***	**Number**	**5-YDSS**	***P***
Sex			0.108			0.920
Female	2255	56.0		4941	52.3	
Male	5405	54.0		6293	52.2	
Age (years)			<0.001			<0.001
<60	4006	59.3		3340	54.5	
≥60	3654	49.3		7894	51.3	
Tumor location			<0.001			<0.001
Antrum/Pylorus	3501	62.9		4684	53.8	
Body	1480	52.1		1424	55.9	
Fundus	2042	49.1		460	51.6	
Overlapping regions	637	32.4		1072	39.0	
Lesser/Greater curvature	–			2433	55.6	
Stomach NOS	–			1161	46.7	
pT stage			<0.001			<0.001
pT1	950	95.7		2713	86.4	
pT2	1412	67.7		1470	71.4	
pT3	1255	53.6		3733	44.0	
pT4a	3549	42.4		2476	26.1	
pT4b	494	26.9		842	21.7	
pN stage			<0.001			<0.001
pN0	2811	80.0		4772	77.0	
pN1	1372	58.1		1908	50.3	
pN2	1488	44.6		1889	37.3	
pN3a	1346	27.5		1847	22.9	
pN3b	643	15.3		818	11.6	
Rpd stage			<0.001			<0.001
Rpd 0	2811	80.0		4772	77.0	
Rpd 1	2329	57.0		2487	52.7	
Rpd 2	1271	32.5		1679	34.5	
Rpd 3	1249	16.3		2296	12.8	
Rnp stage			<0.001			<0.001
Negative lymph nodes	2811	80.0		4472	77.0	
Rnp 1	1851	60.7		1921	55.0	
Rnp 2	1995	33.7		2527	35.4	
Rnp 3	1003	15.0		2014	11.4	
Examined lymph nodes			<0.001			0.322
<16	2303	51.7		5728	52.2	
≥16	5357	55.9		5506	52.3	

5-YDSS, five-year disease-specific survival rate; NOS, not otherwise specified; Rpd, the ratio of positive to detected lymph nodes; Rnp, the ratio of negative to positive lymph node; SEER, the surveillance, epidemiology, and end results.

Table 3

Comparison of the prognostic performance of the N stage, Rpd stage, and the Rnp stage in two patient cohorts.

	AIC	BIC	Likelihood Ratio χ^2 (*P*)
China Cohort			
N stage	53 397.75	53 404.69	1615.05 (<0.001)
Rpd stage	53 182.65	53 189.60	1830.14 (<0.001)
Rnp stage	53 142.09	53 149.04	1870.70 (<0.001)
Model 1[a] + N stage	52 749.92	52 784.64	2270.87 (<0.001)
Model 1 + Rpd stage	52 732.56	52 767.28	2288.23 (<0.001)
Model 1 + Rnp stage	52 716.34	52 751.06	2304.46 (<0.001)
SEER cohort			
N stage	84 431.42	84 438.75	2296.76 (<0.001)
Rpd stage	83 926.84	83 934.16	2801.35 (<0.001)
Rnp stage	83 897.39	83 904.72	2830.79 (<0.001)
Model 2[b] + N stage	83 294.86	83 324.17	3439.32 (<0.001)
Model 2 + Rpd stage	82 936.85	82 966.15	3797.34 (<0.001)
Model 2 + Rnp stage	82 925.42	82 954.73	3808.76 (<0.001)

AIC, Akaike information criterion; BIC, Bayesian information criterion; Rnp, the ratio of negative to positive lymph nodes; Rpd, the ratio of positive to detected lymph nodes; SEER, the surveillance, epidemiology, and end results.
[a]Model 1: T Stage + tumor location + age + exam LNs.
[b]Model 2: T Stage + tumor location + age + tumor size.

Nitti *et al.*[30] reported that the ratio of mLNs, which represents the density of the LN metastasis, was an important prognostic factor in GC patients. At the same time, as eLNs are taken as part of the evaluation, Rpd represents the degree of LN immune response of GC patients and the thoroughness of surgical dissection[6,31]. A retrospective study in Japan demonstrated that Rpd stage was an independent predictor of poor prognosis and had good discriminatory ability[10]. Additionally, many studies have also proven the superiority of Rpd in predicting the prognosis of GC patients[2,5,8,9,26,28,29,32]. A number of studies also found that the TNM staging system combined with Rpd was superior to the AJCC TNM system in terms of homogeneity and discriminatory ability of prognosis, without increasing the complexity[29,33–35]. Rpd combined with ypTNM staging can provide a more accurate prognosis evaluation even for GC patients after neoadjuvant therapy[36–38]. In this study, the Rpd stage also showed a good prognostic prediction ability in both two cohorts.

Although Rpd showed the superiority in prognosis discrimination in GC patients, it ignored the significance of nLNs in prognosis evaluation. A mountain of recent evidences found that even GC patients with pN0 stage also had the possibility of local recurrence or metastasis, since micrometastases in nLNs and isolated tumor cells are considered to be important risk factors for recurrence[3,4,39–42]. The isolated tumor cells and micrometastases in nLNs may be removed with the increasing number of nLNs detected, which may improve the survival[11,43]. Our previous study conducted a retrospective study of 769 GC patients and found that the number of nLNs was an independent predictor of prognosis[3]. Compared with the N stage, the new system, which combined the nLN and TNM staging systems could predict the prognosis more accurately. Subsequently, we also reviewed the impact of the Rnp stage on the prognosis, and found that the Rnp stage showed better performance in prognosis evaluation than the Rpd stage or N stage[11]. In this study, the Rnp stage was also found to be an independent prognostic factor. Compared with the N stage and the Rpd stage, the Rnp stage had smaller AIC and BIC values and a higher likelihood ratio χ^2 value, and this superior effect could also be observed when adjusted with other factors. Rnp includes the comprehensive evaluation effect of nLN and pLN on prognosis, therefore, its clinical significance is more far-reaching than the number of metastatic lymph nodes and Rpd.

Currently, the eighth AJCC TNM staging system recommends the number of eLNs no less than 15 and preferably more than 30[14]. Yuan *et al.*[44] demonstrated that patients with eLN number greater than or equal to 15 had a better prognosis than

Table 4

Comparing the prognostic performance of the N stage, Rpd stage, and the Rnp stage according to the number of examined lymph nodes.

	China Cohort			SEER Cohort		
	AIC	BIC	Likelihood Ratio χ^2 (*P*)	AIC	BIC	Likelihood Ratio χ^2 (*P*)
Examined lymph nodes <16						
N stage	15 255.56	15 261.30	450.03 (<0.001)	40 478.90	40 485.55	1168.95 (<0.001)
Rpd stage	15 240.92	15 246.66	464.67 (<0.001)	40 292.73	40 299.38	1355.12 (<0.001)
Rnp stage	15 224.35	15 230.09	481.24 (<0.001)	40 287.50	40 294.15	1360.35 (<0.001)
Examined lymph nodes ≥16						
N stage	33 811.95	33 818.53	1355.15 (<0.001)	36 835.88	36 842.50	1474.78 (<0.001)
Rpd stage	33 768.05	33 774.63	1399.06 (<0.001)	36 769.71	36 776.33	1540.95 (<0.001)
Rnp stage	33 743.24	33 749.83	1423.86 (<0.001)	36 754.40	36 761.01	1556.27 (<0.001)

AIC, Akaike information criterion; BIC, Bayesian information criterion; Rpd, the ratio of positive to detected lymph nodes; Rnp, the ratio of negative to positive lymph nodes; SEER, the surveillance, epidemiology, and end results.

those with eLN number less than 15 in the same stage. A multicenter study from South Korea found that the number of pLN was substantially correlated with eLN except stage IIB and IIIA, and eLN was an important prognostic factor for stage IIIA patients[45]. Our previous study found that eLN was an independent prognostic factor for patients with stage IIIGC patients, and eLN greater than 31 was associated with a better prognosis[46]. In addition, we found that nLN was significantly correlated with prognosis, and expanded detection of nLN could enhance the accuracy of the TNM system[43]. Bouliaris *et al.*[47] found that the N stage was positively correlated with the number of eLN, while Rpd had no relationship with eLN when the number of eLN less than 15. When the number of eLN greater than 15, both the N stage and Rpd were not correlated with eLN.

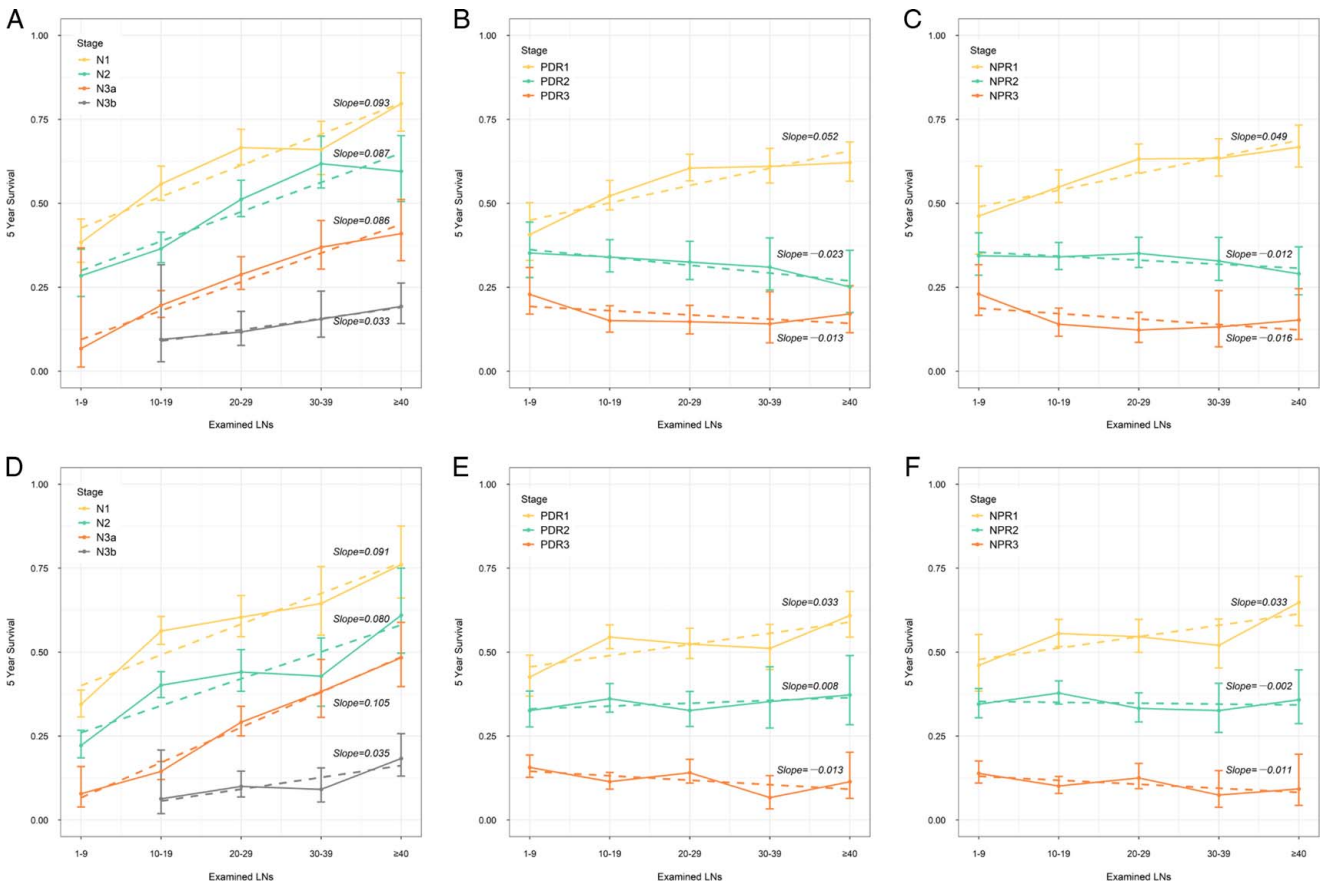

Figure 3. Five-year DSS rate according to the number of examined lymph nodes of patients in China cohort classified by the N stage of the eighth edition TNM staging system (A), the Rpd staging system (B) and the Rnp staging system (C). Five-year DSS rate according to the number of examined lymph nodes of patients in Surveillance, Epidemiology, and End Results cohort classified by the N stage of the eighth edition TNM staging system (D), the Rpd staging system (E) and the Rnp staging system (F). Slope: corresponds with estimated Five-year DSS rate gain (%) per subsequent 10 examined LNs. Rpd, the ratio of positive lymph nodes to detected lymph nodes; Rnp, the ratio of negative lymph nodes to positive lymph nodes.

That indicated that Rpd was independent of the number of eLNs. In this study, the survival changing trend in two cohorts showed that survival rates increased in a linear manner with 10 additional eLNs in N stages, especially for patients in N1–N3a stages. Nonetheless, when we classified patients into Rpd and Rnp stages, the survival changes were minimal except for a slight increase in Rpd1 and Rnp1 patients. Regardless of the number of eLNs, Rnp stage had smaller AIC and BIC values than N stage and a higher likelihood ratio χ^2 value, indicating that it was more suitable for predicting the prognosis in each situation of lymphadenectomy. And the same results were obtained in the SEER database. Therefore, we believed that Rpd is more meaningful prognostic indicator for GC that is applicable to a wider range of people.

This study has several limitations. Firstly, this study was a retrospective study and the selection bias may occur. We were unable to gather information on the state of specific individuals, such as autoimmunity. Secondly, our study included patients from 2000 to 2012, and treatment may not be exactly the same as it is now. Finally, we utilized the X-tile approach for classification. This approach of classification is essentially solely based on our cohort, and its predictive significance may not be evident for data from other cohorts or from data from different countries. Future verification will also require more external data. Therefore, multicenter prospective studies with more complete information are urgently required.

Conclusion

The Rnp stage is an independent prognostic factor for GC patients. The prediction model established by Rnp combined with T stage, tumor site, age, and other prognostic factors could evaluate the prognosis of GC patients. Rnp stage had no effect on the number of eLN and showed better prediction than the N stage and the Rpd stage. Prospective studies with a larger sample size need to be carried out to better predict the prognosis of GC patients and provide more precise treatment.

Ethical approval

This study was approved by Medical Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (Approval number: bc2018037).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

X.W., Z.W., R.Z., H.X., Z.Z., H.L., and J.D.: study conception and design. X.W., P.W., W.W., and Z.S.: data collection and assembly. All authors participated in the data analysis and interpretation, and manuscript writing. All authors read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

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Guarantor

Jingyu Deng.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The SEER datasets used in this study can be freely available at the following address: https://seer.cancer.gov/.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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