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Prognostic Performance of Three Lymph Node Staging Systems in Patients After D2 Lymphadenectomy for Gastric Cancer

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Background: Accurate staging of lymph node (LN) status is essential for predicting prognosis in patients with gastric cancer. Recent proposals suggest that lymph node ratio (LNR) and log odds of metastatic lymph nodes (LODDS) may have superior accuracy in predicting survival by minimizing stage migration. The aim of the present study was to compare the prognostic performances of the UICC (pN), LNR and LODDS staging systems and incorporate the optimal system into a nomogram for predicting individual survival in patients with resectable gastric cancer.

Methods: The study cohort comprised of 423 patients who had undergone D2 lymphadenectomy. The discriminatory powers of the different LN staging systems were compared using the concordance index (C-index). The optimal system was incorporated into a prognostic nomogram with other independent prognosticators, and bootstrap validation was performed.

Results: When LN status was assessed as a continuous variable, the LNR system (C-index: 0.712) was superior to pN (C-index: 0.695) and LODDS (C-index: 0.704). Age, LNR, and

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preoperative serum CA 19-9 and CA 125 were incorporated into a nomogram for predicting 2-year overall survival. Internal validation of the nomogram revealed good predictive abilities, with a bootstrap-corrected concordance index of 0.704.

Conclusion: Overall, LNR was the optimum predicator of survival in patients with resectable gastric cancer on the basis of LN status. LNR was incorporated into a nomogram along with age and preoperative serum CA 19-9 and CA 125. Internal validation confirmed the predictive ability of this nomogram.

Key words: Gastric cancer – TNM staging – Lymph node ratio – Log odds of metastatic lymph nodes – Prognostic discrimination – Nomogram

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related death worldwide.[1] At present, advanced tumor invasion and lymph node (LN) involvement are the best indicators of poor prognosis in patients with resectable gastric cancer.[2,3]

Several LN staging systems have been proposed for predicting prognosis in patients with gastric cancer. The numerical node staging system (pN), which was based on the number of metastatic lymph nodes (MLN), is the method most commonly used for nodal staging in clinical practice.[4] However, this method does not account for the number of total harvested nodes (THNs) at the time of surgery, which might affect patient outcomes.[5] The LN ratio (LNR), defined as the ratio between MLN and THN,[6–8] and the log odds of metastatic lymph nodes (LODDS), defined as the log of the ratio between the number of MLNs and the number of negative lymph nodes, were established to avoid stage migration and has been shown to be more reliable than the pN system for prognostic stratification.[9–13] Despite these findings, it remains inconclusive as to whether LNR and LODDS can replace pN staging in terms of accuracy and they are not yet widely accepted.

To address these issues, we compared the performances pN, LNR and LODDS staging and incorporated the optimal system into a nomogram with other significant prognostic indicators for predicting survival in patients with resectable gastric cancer.

Methods

Patient selection and treatments

We identified 540 patients who had been diagnosed with gastric cancer and had undergone D2 lymphadenectomy between December 2012 and July 2014 at The Lan Zhou University Second Hospital. The inclusion criteria were as follows: (1) histologically confirmed as IB-IIIC gastric adenocarcinoma; (2) undergone R0 resection for gastric cancer; and (3) available follow-up data. The following exclusion criteria were applied: (1) death within 90 days of surgery; (2) presence of residual macroscopic or microscopic tumors; and (3) treated with neoadjuvant chemo/radiotherapy or adjuvant radiotherapy. Adjuvant chemotherapy was routinely advised for patients with Stage II-III tumor. This study was approved by the Ethics Committee of Lan Zhou University Second Hospital.

Statistical analysis

Analyses were performed using SPSS v.19.0 and R v.3.1.2 (R Project for Statistical Computing: http://www.r-project.org) statistical packages. Spearman's rank correlations were performed to evaluate relationships within pN, LNR and LODDS variables. Overall survival (OS) was calculated from the date of surgery until final follow-up or death from any cause. Univariate and multivariate Cox regression analyses were performed to assess the relationships between clinicopathologic factors and OS; variables that were identified as statistically significant in the univariate Cox model ($P < 0.05$) were included in the multivariate Cox model. pN, LNR and LODDS were included in separate Cox models to avoid multicollinearity.[14] Restricted cubic splines were used to examine the linearity assumption in continuous variables.[15] An appropriate transformation was chosen when the relationship was apparently nonlinear. The final model was obtained by performing a backward stepwise selection. The discriminative powers of the three LN staging systems were assessed using concordance indices (C-index).[16] The best performing LN staging system was incorporated into a nomogram with other selected prognostic indicators. Discrimination and calibration were performed to evaluate the nomo-

Table 1 Clinicopathologic characteristics of the study population

Clinicopathologic characteristic	Mean parameter value or no. of patients	SD or % patients
Age, y	56.1	10.6
Gender		
Male	326	77.1
Female	97	22.9
Preoperative CEA, U/mL	12.0	39.1
Preoperative CA 19-9, U/mL	45.8	149.0
Preoperative CA 125, U/mL	16.2	23.9
Tumor size, cm	4.3	2.5
Tumor location		
Cardia	70	16.5
Fundus/corpus	159	37.6
Antrum	194	45.9
Differentiation		
Moderate/high	176	41.6
Poor/low	247	58.4
Lymphovascular invasion		
Yes	334	79.0
No	89	21.0
Perineural invasion		
Yes	223	53.9
No	195	46.1
Depth of tumor invasion		
T1	47	11.1
T2	60	14.2
T3	0	0
T4	316	74.7
MLN	5.0	6.4
N0	158	37.4
N1	68	16.1
N2	68	16.1
N3	129	30.5
THN	17.1	7.6
≤15	197	46.6
16–20	120	28.4
>20	106	25.0
LNR	0.3	0.3
LODDS	−1.5	1.8
Adjuvant chemotherapy		
Yes	301	71.2
Single fluorouracil	60	7.1
Fluorouracil plus oxalipaltin	211	49.9
Other	30	14.2
No	82	19.4
Unknown	40	9.4

gram.[17] Bootstrap-validation was performed to quantify any model overfit.

Results

Table 1 summarizes patients' characteristics. The study cohort consisted of 423 patients. Among them 265 (62.6%) patients had LN metastasis; the retrieval of >15 LNs had been achieved in 226 (53.4%) of patients. The median follow-up period was 18.3 months (IQR: 9.5–27.2 months).

The value of LNR increased as the number of MLN increased, suggesting a close correlation between these two parameters ($r = 0.879$). However, the relationship was not linear and the value of LNR declined as THN >15 (Fig. 1A). A similar relationship was observed between LODDS and MLN ($r = 0.888$; Fig. 1B). In contrast, the correlation between LODDS and LNR remained approximately linear ($r = 0.963$) with the exceptions of the extremes (Fig. 1C)

Multivariate cox regression analyses revealed that LNR had superior prognostic value (C-index: 0.712) compared to both pN (C-index: 0.695) and LODDS (C-index: 0.704). Furthermore, LNR remained the best performing system in patients with ≤15 or >20 LNs retrieved (C index: 0.647 and 0.725, respectively) when stratified by THN. However, in patients with 16 to 20 retrieved LNs, LODDS had the best prognostic performance (C index: 0.656; Table 2).

To provide an intuitive and quantitative method to better stratify patients with different prognosis, a nomogram incorporating LNR and other significant prognostic factors (age, CA 19-9 and CA 125) was established. The nomogram was able to predict each patient's prognosis individually: the higher the total score, the poorer the prognosis. For example, a 60 year-old patient (20 points) with an LNR of 0.2 (10 points), a serum CA 19-9 level of 300 (10 points) and a serum CA 125 level of 60 (22 points) would have a total of 62 points, yielding an estimated 2-year OS of 38%.

The unadjusted C-index for OS prediction was 0.712 and the bootstrap-corrected C-index was 0.704, which revealed minimal evidence of model overfit. The calibration plot showed close agreement between the actual 2-year OS values in the study population and the predicted OS according to the nomogram (Fig. 2B). Furthermore, the patients were divided evenly into 3 subgroups based on the tertiles of the total points and the outcomes within the subgroups were compared using the Kaplan-Meier curves. The results showed that each group represented a distinct prognosis (Fig. 2C).

Discussion

Accurate staging of LN status is essential for predicting prognosis and planning treatments in patients with gastric cancer. In 2010, Sun *et al* reported that LODDS was superior to both the UICC pN and ratio-based LNR staging systems for

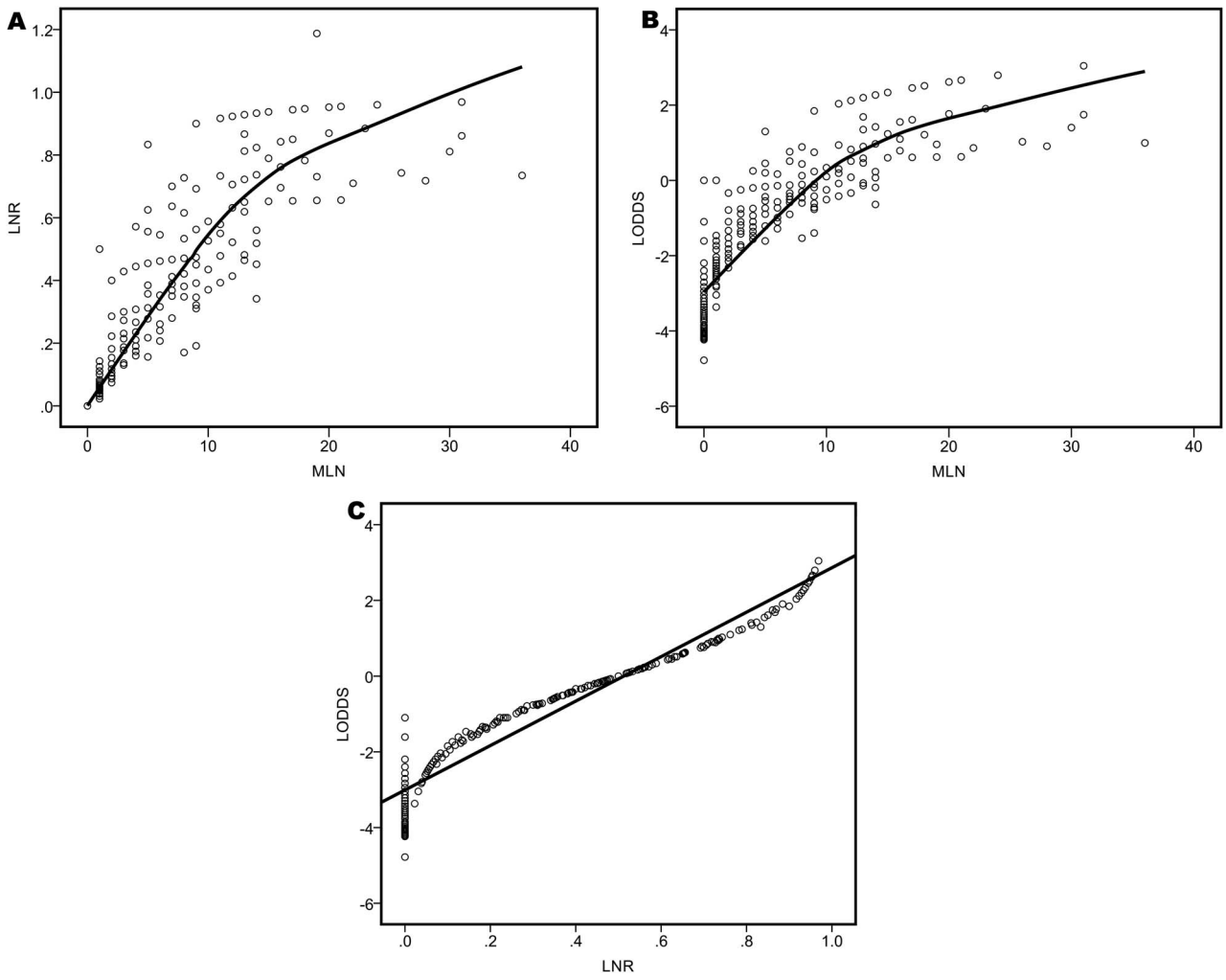

Fig. 1 Comparisons between different LN number-based and ratio-based staging systems in patients with resectable gastric cancer: Distribution curves of (A) LNR versus MLN; (B) LODDS versus MLN; (C) LODDS versus LNR.

prognostic assessment in patients after R0 resection.[12] However, subsequent reports have proved contradictory: whereas some studies supported their findings,[9–13] others did not find a superiority of LODDS over pN or LNR in discriminating prognoses in these patients.[18–20] The inconsistencies between the various studies may be due to differences in the statistical methods for analysis. All three LN staging systems are closely correlated, therefore studies using stepwise regression to determine the highest performing staging system have been inappropriate.[10,12,18] In addition, there is still no consensus on the ideal cutoff values for the three LN staging systems, and the choice of cutoff values between different studies may be affected by the size of the study cohort and the clinicopathologic characteristics of the patients.

Table 2 Prognostic performances of pN, LNR and LODDS based on C-index

	Number of LNs examined, C-index			
Variable	All	≤15	16–20	≥21
pN	0.695	0.633	0.652	0.705
LNR	0.712	0.662	0.656	0.745
LODDS	0.704	0.647	0.657	0.722

Several reports have suggested that the prognostic value of LN staging can be improved by treating LN scores as continuous variables rather than categorical variables.[9,13] Therefore, we adopted these approaches to assess pN, LNR, and LODDS performances in the present study and the results demonstrated that LNR showed the highest prog-

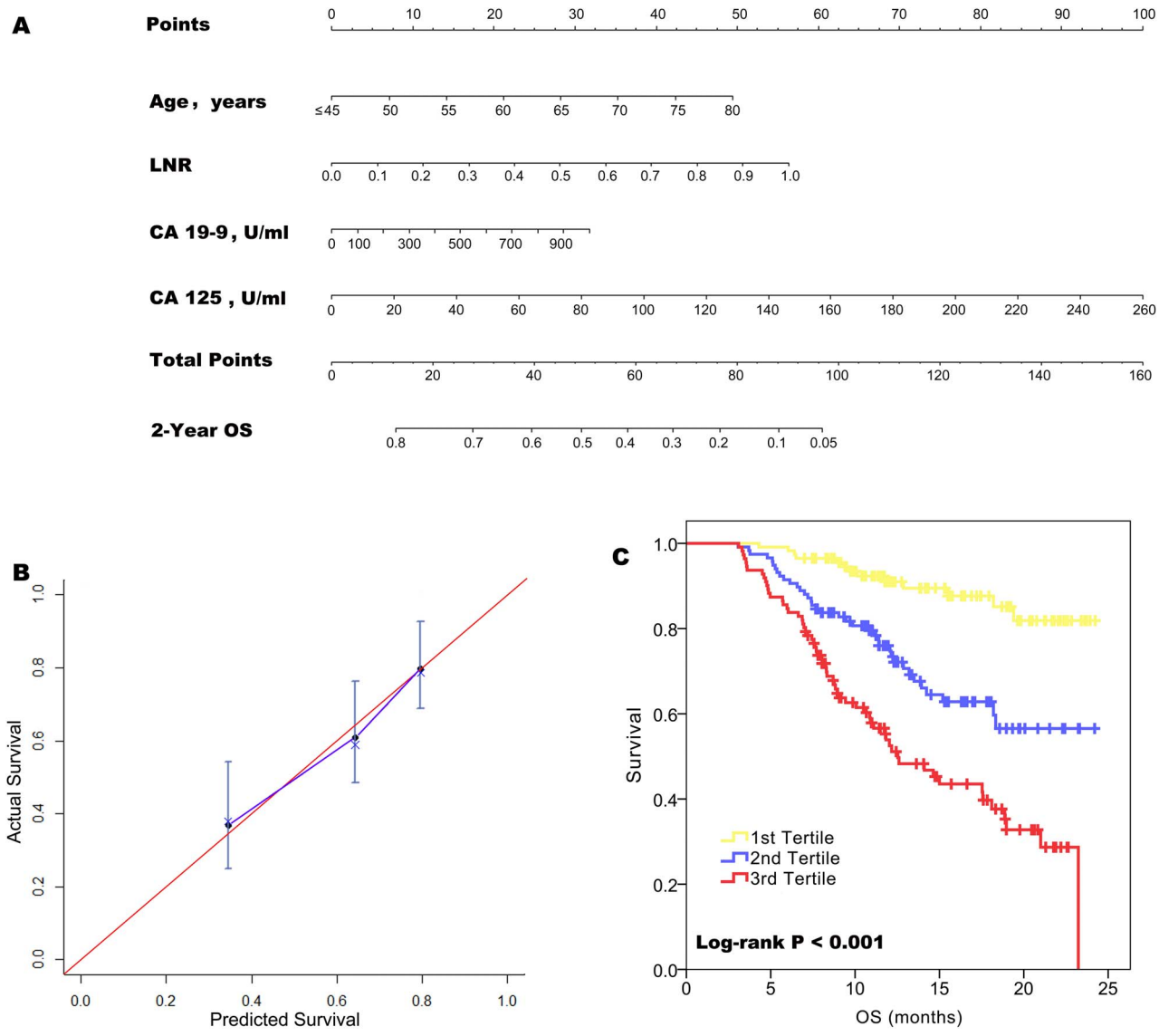

Fig. 2 Prognostic nomogram for predicting OS in patients with resectable gastric cancer: (A) Predictive nomogram for OS, incorporating age, LNR, and preoperative serum CA 19-9 and CA 125. (B) The calibration plot for nomogram-predicted survival shows close correlation with the ideal 45-degree reference line. (C) Kaplan-Meier curves demonstrating OS in patients grouped according to the tertiles of nomogram-predicted OS. Each group represents a distinct prognosis.

nostic accuracy in patients with R0 resected gastric cancer. Although the underlying mechanisms remain unknown, a possible explanation is that LNR may better mimic the actual mathematic interaction between MLNs and THNs on survival among this cohort. This finding was verified by bootstrap-validation.

Investigations to determine the prognostic accuracy of LN staging systems according to the number of THN have been conflicting: The studies by Sun *et al*[12] and Wang *et al*[13] who found that LODDS constantly outperformed other LN systems irrespective of the number of THN. In contrast, Xu *et al*[19] found that LODDS only gave the best performance if THN <10; LNR was better when THN >15; however, when Kaplan-Meier curves were used instead of ROC curves, pN showed the best discriminatory accuracy for THN >15. To date, Spoverato *et al*[9] are the only investigators known to have incorporated pN, LNR and LODDS as continuous variables into a multivariate analysis to adjust for clinicopathologic factors. Their results indicated

that LNR was the most reliable when the number of harvested LNs was ≤15 but that LODDS achieved the same C-index when THN >15.[9] The present study applied the same methodology and obtained similar findings. The following factors may account for the inconsistencies: differences in statistical methods can lead to contradictory findings, even within the same study; for example, the study by Xu *et al*[19] discussed above. The distribution of clinicopathologic characteristics can vary when stratified by THN; for example, higher THN values have been associated with younger patients, increasing stage and higher hospital volumes.[21,22] Therefore, further studies need to be conducted using methodologically sound approaches, such as matched case-control logistic regression, to investigate the prognostic performances of different LN staging systems within different THN subgroups.[23]

Kim *et al*[24] constructed a nomogram incorporating patient age, gender, pT, tumor site and LNR to predict OS and showed it had better discriminatory power than both the UICC staging system and the nomogram established by the Memorial Sloan Kettering Cancer Centre.[25] The current nomogram achieved a similar level of discrimination to that of Kim *et al*.[24] Our cohort was selected over a narrower admission period (December 2012–July 2014) and the treatment regimens had been relatively standardized; however, only short-term survival (2-year OS) was assessed. Kim *et al* showed that pT was a strong predictor of OS, whereas in the present study pT failed to predict OS independently, possibly due to the small number of patients with T1/2 disease. An advantage of the nomogram in the present study over that of Kim *et al*. was that it incorporated preoperative serum values of CA 19-9 and CA 125. Previous studies have demonstrated that these factors were useful prognostic markers in patients who had undergone curative resection.[26,27] Further studies are still required to validate the value of incorporating CA 19-9 and CA 125 in prognostic nomograms.

In summary, this study has provided strong evidence that LNR was superior to other LN based staging systems in predicting survival outcome in patients who had undergone D2 resection. In addition, LNR was developed into a nomogram with age, and preoperative serum CA 19-9 and CA 125 to refine the prediction of OS in these patients. The nomogram was internally validated, and it may become a useful tool in prognosis, follow-up and treatment programming if externally validated.

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