EBioMedicine 41 (2019) 276–285

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Comparison of three lymph node staging schemes for predicting the outcome in patients with small bowel adenocarcinoma: A population-based cohort and international multicentre cohort study

Yang-Yang Zhou [a,1], Xiao-Jing Du [b,1], Chi-Hao Zhang [c,1], Thomas Aparicio [d,1], Aziz Zaanan [e], Pauline Afchain [f], Li-Ping Chen [g], Sun-Kuan Hu [b], Pei-Chen Zhang [h], Ming Wu [b], Qing-Wei Zhang [i,*], Hong Wang [a,*]

[a] Department of Rheumatology and Immunology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China
[b] Department of Gastroenterology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China
[c] Department of General Surgery, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiao Tong University, Baoshan 201999, Shanghai, China
[d] Gastroenterology department, Saint Louis Hospital, APHP, University Paris Diderot, Paris, France
[e] Gastroenterology and Digestive Oncology department, Georges Pompidou Hospital, APHP, Paris, France
[f] Oncology department, Saint Antoine Hospital, APHP, Paris, France
[g] Chemical Biology Research Center, College of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou, Zhejiang 325000, China
[h] Department of Gastrointestinal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China
[i] Division of Gastroenterology and Hepatology, Key Laboratory of Gastroenterology and Hepatology, Ministry of Health, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, 145 Middle Shandong Road, Shanghai 200001, China

ARTICLE INFO

Article history:
Received 30 November 2018
Received in revised form 6 February 2019
Accepted 19 February 2019
Available online 26 February 2019

Keywords:
Small bowel adenocarcinoma
Log odds of positive lymph nodes
Lymph node ratio
Number of positive lymph nodes
Prognosis
Multicentre cohort

ABSTRACT

Background: The prognostic roles of three common lymph node staging schemes, number of positive lymph nodes (pN), lymph node ratio (LNR) and log odds of positive lymph nodes (LODDS) in small bowel adenocarcinoma (SBA) are unclear. We assessed their prognostic ability in SBA.
Methods: A total of 2128 patients diagnosed with SBA between 1988 and 2010 from the Surveillance, Epidemiology, and End Results (SEER) database and 186 patients from 15 hospitals in France and China were identified. We evaluated the prognostic ability of the schemes in both continuous and stratified patterns using R^2, Harrell's C, and time-dependent receiver operating characteristic curve analyses.
Findings: For continuous pattern, the LODDS had a better capacity of discrimination and higher accuracy of prognosis than pN and LNR. Similarly, the stratified LODDS classification had a better performance of discrimination and higher accuracy of prognosis than the pN and LNR classification. The multivariable model using the LODDS classification also showed superiorly predictive accuracy and discriminatory capacity to those of the 7th and, 8th TNM node and LNR classification. These results were fully validated in an independent international multicentre cohort.
Interpretation: The LODDS scheme showed a better prognostic performance than the LNR or pN schemes in patients with SBA regardless of continuous or stratified pattern. The LODDS scheme could serve as an auxiliary to lymph node staging systems in future revisions of the American Joint Committee on Cancer (AJCC) manual.
Fund: This work was funded by the Zhejiang Province Natural Science Fund of China.

1. Introduction

Small bowel cancers are rare malignant tumors, comprising around 3·2% of cancers of the digestive system [1]. They include tumors derived from diverse histology, mainly carcinoids, adenocarcinomas, lymphomas, and sarcomas [2]. Among them, small bowel adenocarcinoma (SBA) is the most common histology of tumors in the United States, with a rising incidence not only in North American and Western Europe, but also in Asia [3,4]. Surgical excision remains the foundation of therapy for SBA manifesting as locoregional disease [5]. The rarity of SBA hinders further understanding of its molecular mechanism, resulting in current bottlenecks in the multidisciplinary management of patients after surgery [2,6]. Thus, there is an urgent need to identify prognostic performance metrics.

* Corresponding authors.
E-mail addresses: mylikedlam@sjtu.edu.cn (Q.-W. Zhang), wh@wzhealth.com (H. Wang).
[1] Yang-Yang Zhou and Xiao-Jing Du, Chi-Hao Zhang, Thomas Aparicio contributed equally to this work.

https://doi.org/10.1016/j.ebiom.2019.02.043

Research in context

Evidence before this study

We search the literature on the treatment and survival of small bowel adenocarcinoma and evaluation of lymph node metastasis in patients with small bowel adenocarcinoma in PubMed database. We found that lymph node metastasis has been considered as one of the most robust prognostic markers for small bowel cancer using multivariate analysis. However, the role of the number of positive lymph nodes, lymph node ratio and log odds of positive lymph nodes in small bowel adenocarcinoma are ill-defined.

Added value of this study

This large study involved two different cohorts to compare the predictive capacity of three lymph node staging schemes for the survival of small bowel adenocarcinoma patients. We found a superior prognostic ability of the log odds of positive lymph nodes scheme in patients with small bowel adenocarcinoma from the Surveillance, Epidemiology, and End Results database, and uniquely verified this finding in a cohort of patients from France and China.

Implications of all the available evidence

Lymph node metastasis is an important prognostic indicator for cancers. The rarity of small bowel adenocarcinoma hinders multidisciplinary management of patients with surgery. The log odds of positive lymph nodes scheme could provide surgical guidelines to improve the prediction of prognosis of small bowel adenocarcinoma and could be included in the lymph node staging system in future revisions of the American Joint Committee on Cancer (AJCC) manual.

In addition to the presence of distant metastasis [7], the most prognostic factor for patients with SBA, lymph node metastasis was also shown to be an important independent prognostic factor for SBA in multivariate analysis [8,9]. Adequate lymph node histopathological assessment is critical for accurate pN staging [10]. In order to avoid stage migration effects, adequate evaluation of the lymph node status is important. However, 82% of patients with SBA did not have adequate lymph nodes examination in our previous study based on a minimal of 17 retrieved lymph nodes. In this context, we tried to identify new measures of lymph node status with the combination of the number of retrieved lymph nodes.

To the best of our knowledge, two measures, namely lymph node ratio (LNR), log odds of positive lymph nodes (LODDS) have been proposed. LNR is calculated by dividing the number of positive lymph nodes by the total number of excised lymph nodes. LNR provides important guidance regarding the survival of patients with SBA [11]. Few intensive studies on LNR have shown its superiority in guiding the prognosis of SBA over that of the numbers of positive lymph nodes (pN). LODDS, calculated as the log of the ratio between the number of positive and negative lymph nodes, has been applied to predict the prognosis of several tumors [12–15]. There is little clinical evidence demonstrating the role of LODDS in SBA and the most suitable scheme to describe prognosis of SBA remains ill-defined.

Therefore, this study compared the prognostic ability of the lymph node schemes in SBA by means of the population-based Surveillance, Epidemiology, and End Results (SEER) database with patients diagnosed between 1988 and 2010 and an international multicentre cohort of 15 hospitals that was built to validate our findings.

2. Materials and methods

2.1. Data source and patients

Data of patients with SBA during 1988–2010 were obtained from the SEER database. The patient eligibility criteria were as follows: (1) primary tumor located in the small intestine; (2) ≥18 years of age; (3) treatment with primary tumor surgery; (4) without radiotherapy for the first round of therapy; (5) with close follow-up; (6) at least one lymph node was retrieved; (7) histologically-confirmed SBA. Another independent international multicentre cohort of 186 patients with SBA from 15 hospitals in France and China from 1998 to 2010 with the same inclusion and exclusion criteria was developed for the validation of the LNR and LODDS schemes. In this study, cause-specific survival (CSS) was defined as death caused by SBA and overall survival (OS) as death regardless of any causes. The primary outcome was CSS with OS and CSS considering competing death due to non-SBA death as the secondary outcome.

2.2. Definitions of classification

To describe lymph node status more precisely, we attempted to evaluate the prognostic performance of the American Joint Committee on Cancer (AJCC) 7th edition N stage (7th pN classification), AJCC 8th edition N stage (8th pN classification), LNR classification, and LODDS classification in patients with SBA. According to the 7th edition of AJCC TNM staging, N0 was defined as no regional lymph node metastasis, N1 as metastasis in one to three regional lymph nodes and N2 as metastasis in four or more regional lymph nodes. However, the definition of regional lymph nodes changed in 8th edition. N1 was redefined as one or two regional lymph nodes and N2 as more than two positive nodes [16]. LODDS was defined as $\log_e[(pN + 0{\cdot}5)/(nN + 0{\cdot}5)]$ [17], where pN is the number of positive lymph nodes and nN is the number of negative nodes retrieved.

2.3. Statistics

The correlation of continuous LNR, pN, and LODDS were calculated using Spearman coefficients. The relationship between LNR, pN or LODDS and SBA survival were determined by univariate Cox regression model with a restricted cubic spline function for each variable. The cutoff points to define LNR or LODDS lymph node staging classification were determined using X-tile software [18], which provides a single, global assessment of every possible way of dividing a population into low-, medium-, and high-level marker expression. The three optimal divisions of the data were identified by selecting the highest X^2 value with statistical significance assessed by using the cutoff point derived from a training set to parse a separate validation set with standard log-rank tests.

The prognostic performances for CSS of the lymph node staging schemes were compared. Regarding the overall model performance assessment, R^2 demonstrated the survival variability that could be explained by a predictive model [19], and high R^2 value indicated superiority of prognostic model. Harrell's C statistic with corresponding 95% confidence intervals (95%CIs), as a measure of discriminatory power, was used to evaluate the proportion of positive predictive value [20]. The bootstrap method ($N = 1000$) was used to calculate bias-corrected Harrell's C statistic [21]. To evaluate the discrimination power of the three lymph node schemes for time-dependent survival, the area under receiver operating characteristics (AUROC) of time-dependent receiver operating characteristic curve (tdROC) analyses over 12 years were made for CSS, OS, and competing risk model, which dynamically displayed the prognostic superiority of the LODDS scheme [22].

For the extracted patients, each incomplete variable was imputed by a separate model based on fully conditional specifications [23].

Multivariable Cox regression models were built to jointly assess the prognostic ability of the three lymph node staging schemes and other possible prognostic indicators. Each candidate variable with a *P*-value <0·1 in the univariate model was included in the multivariate model.

Sensitivity analyses were performed to assess our results. Firstly, the prognostic performance for OS using a Cox regression model and CSS using regression modeling of subdistribution functions in consideration of competing risk of non-SBA death for the three lymph node staging schemes were compared. Secondly, the established novel LNR or LODDS classification schemes were validated in the cohort of patients diagnosed from 2011 to 2014. Thirdly, a multivariable Cox regression model was used to analyze prognostic performance of the three node staging schemes and other possible prognostic predictors after excluding patients with missing values. All data analyses and drawings were completed using R software 3·4·3 (http://www.r-project.org).

3. Results

3.1. Characteristics of patients

A total of 2128 qualified participants with SBA diagnosed from 1988 to 2010 in the SEER database were enrolled in this study (Supplementary Fig. 1). The clinical characteristics and distributions of different lymph node staging systems are described in Table 1. In SEER database, 172 (8·1%) patients had SBA of stage I, 699 (32·9%) stage II, 830 (39·1%) stage III, 422 (19·9%) stage IV with the five-year CSS rates of stage I to IV being 82·4%, 58·7%, 31·3%, and 7·85%, respectively (Supplementary Fig. 2). Meanwhile, a total of 186 patients from an international multicentre cohort was included for the independent validation of our findings (Table 1).

3.2. Characteristics of the lymph node staging schemes

The relationship between LNR and pN, LODDS and LNR, and LODDS and pN are displayed as scatterplots in Supplementary Fig. 3. The LODDS was more highly correlated with LNR than with pN ($r = 0·885$ versus $r = 0·757$). The relationship between log hazard ratio and LODDS and between LNR and pN were shown in Supplementary Fig. 4a-c. In the respective lymph node schemes, the mortality risk rose as the value of LODDS, LNR or pN increased, while the trends of function were not linear simply. Moreover, it was suggested from restricted cubic spline analyses that the mortality risks also increased as LODDS increased among patients with no positive lymph node involved (Supplementary Fig. 4d).

3.3. Prognostic abilities of LODDS, LNR, and pN in the SEER database

As shown in Table 2, the overall performance of the LODDS had a higher R^2 value (0·184) than LNR (0·158) or pN (0·068) schemes, indicating its superiority as a prognostic factor. Measured by Harrell's C statistic, the LODDS (0·673; 95%CI: 0·656–0·691) could provide a better discriminatory capacity than those of the pN (0·629; 95%CI: 0·614–0·645) and LNR (0·655; 95%CI: 0·640–0·671).

Analyses based on AUC measures (Table 2, Supplementary Table 1) showed LODDS (five-year: 74·61%; 95%CI: 72·33%–76·89%) provided better discriminatory capacity than those of pN (five-year: 69·70%; 95%CI: 67·42%–71·97%) and LNR (five-year: 71·88%; 95%CI: 69·70%–74·06%), which was consistent with results measured by the Harrell's C indices. As shown in Fig. 1, the LODDS had higher one-, three-, five-, seven-, and ten-year AUROC for CSS, indicating its better performance for determining the prognosis of patients with SBA. The sensitivity analysis using OS as outcome instead of CSS still identified the superiority of the LODDS over LNR or pN (Supplementary Table 1, Supplementary Table 2 and Supplementary Fig. 5) as measured by R^2, Harrell's C, and AUC. Meanwhile, we also compared the R^2, Harrell's C, and AUC values of the three lymph node staging schemes in the competing risk model in consideration of a competing risk of non-SBA death with similar results (Supplementary Table 1, Supplementary Table 3 and Supplementary Fig. 6). Besides, the sensitivity analysis was also performed after eliminating SBA patients with systemic metastases. Results indicate that LODDS had a higher R^2 (0·164), Harrell's C (0·665; 95%CI: 0·647–0·684), and five-year AUC (72·95%, 95%CI: 70·49%-75·40%) than those of pN and LNR, reflecting its better discriminatory capacity and prognostic performance (Supplementary Table 4).

Table 1
Clinical characteristics of for patients with small intestine adenocarcinoma from the Surveillance, Epidemiology, and End Results database and multicentre cohort.

Factor		SEER database	Multicentre cohort
		N = 2128	*N* = 186
Sex	Male	1102 (52%)	89 (48%)
	Female	1026 (48%)	97 (52%)
Race	White	1659 (78%)	/
	Black	344 (16%)	/
	Others	125 (6%)	/
Age (Years)	≤ 60	907 (43%)	84 (45%)
	> 60	1221 (57%)	102 (55%)
Marriage	Yes	1259 (61%)	/
	No	806 (39%)	/
Size	≤ 2	233 (13%)	/
	≤ 2	365 (20%)	/
	≤ 3	619 (35%)	/
	>5	574 (32%)	/
T category[a]	T1	103 (5%)	4 (2%)
	T2	118 (6%)	23 (12%)
	T3	900 (47%)	84 (45%)
	T4	777 (41%)	74 (40%)
M stage	M0	1706 (80%)	165 (89%)
	M1	422 (20%)	21 (11%)
Tumor site	Duodenum	839 (46%)	126(68%)
	Ileum	411 (23%)	25(13%)
	Jejunum	539 (30%)	35(19%)
	Others	34 (2%)	/
Grade	I/II	1201 (61%)	125 (67%)
	III/IV	778 (39%)	61 (33%)
Total no. of nodes retrieved	Median (IQR)	8 (4, 14)	6 (4,11)
No. of positive nodes (pN)	Median (IQR)	1 (0, 3)	0 (0,2)
LNR	Median (IQR)	0·083 (0, 0·454)	0 (0,0·362)
LODDS	Median (IQR)	−1·609 (−2·617, −0·167)	−1·807 (−2·565,−0·511)
7th pN classification	N0	980 (46%)	98 (53%)
	N1	753 (35%)	57 (31%)
	N2	395 (19%)	31 (17%)
8th pN classification	N0	980 (46%)	98 (53%)
	N1	604 (28%)	45 (24%)
	N2	544 (26%)	43 (23%)
LNR classification	LNR1 (≤0·02)	981 (46%)	98 (53%)
	LNR2 (0·02–0·47)	628 (30%)	48 (26%)
	LNR3 (>0·47)	519 (24%)	40 (21%)
LODDS classification	LODDS1 (≤ − 1·89)	925 (43%)	38 (36%)
	LODDS2 (−1·89– −0·51)	589 (28%)	33 (31%)
	LODDS3 (> − 0·51)	614 (29%)	36 (34%)

Among all 2128 patients in SEER database, the number of missing items for marriage, tumor site, size, tumor category and grade were 63 (3%), 305 (14%), 337 (16%), 230 (10.8%) and 149 (7%), respectively.
LNR: lymph node ratio; LODDS: log odds of positive lymph nodes; pN: number of positive nodes.
[a] Tumor category and 8th pN were graded according to the 8th edition of the tumor node metastasis (TNM) classification of malignant tumors proposed by the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC), whereas 7th pN was graded according to the 7th edition of the TNM staging manual. pM indicates metastatic disease pathologically coded 85 in "EOD 10-extent (1988–2003)" of SEER data.

Table 2
Univariable analysis for overall prognostic performance of node staging schemes for small intestine adenocarcinoma for cause-specific survival.

	SEER database				Multicentre cohort			
	R^2	Harrell's C	Bootstrap	AUC (5 year)	R^2	Harrell's C	Bootstrap	AUC (5 year)
pN	0·068	0·629 (0·614–0·645)	0·629	69·70 (67·42–71·97)	0·049	0·599 (0·545–0·653)	0·599	64·83 (56·11–73·56)
LNR	0·158	0·655 (0·640–0·671)	0·655	71·88 (69·70–74·06)	0·110	0·624 (0·570–0·678)	0·623	67·06 (58·87–75·25)
LODDS	0·184	0·673 (0·656–0·691)	0·674	74·61 (72·33–76·89)	0·131	0·647 (0·587–0·707)	0·646	69·09 (59·88–78·30)
7th pN classification	0·129	0·626 (0·611–0·642)	0·627	69·21 (66·96–71·46)	0·077	0·604 (0·550–0·657)	0·600	66·05 (57·71–74·39)
8th pN classification	0·130	0·626 (0·611–0·642)	0·626	69·51 (67·25–71·77)	0·069	0·593 (0·540–0·646)	0·583	64·83 (56·11–73·56)
LNR classification	0·157	0·644 (0·629–0·660)	0·644	70·64 (68·47–72·82)	0·090	0·615 (0·561–0·668)	0·611	65·98 (57·59–74·37)
LODDS classification	0·178	0·656 (0·640–0·671)	0·656	72·30 (70·13–74·46)	0·120	0·629 (0·574–0·683)	0·627	67·61 (59·12–76·10)

LNR: lymph node ratio; LODDS: log odds of positive lymph nodes; pN: number of positive nodes.

3.4. Prognostic abilities of LODDS, LNR, and pN classification in the SEER database

To comprehensively and reasonably compare the lymph node staging schemes, we grouped continuous variables of the LODDS and LNR schemes into three classification levels using the minimal *P*-value approach in the X-Tile software. LNR was classified into three group: 981 (46%) in LNR1 (≤0·02), 628 (30%) in LNR2 (0·02–0·47), and 519 (24%) in LNR3 (>0·47). A novel three-subgroup LODDS classification was determined using two LODDS cut-off points: 925 (43%) in LODDS1 (≤ − 1·89), 589 (28%) in LODDS2 (−1·89– − 0·51), and 614 (29%) in LODDS3 (> − 0·51) (Table 1).

As shown in Supplementary Fig. 7, increased LODDS or LNR values were associated with shorter survival times and higher mortalities. To compare the prognostic abilities of the three lymph node staging schemes, we plotted and compared the survival rates stratified by LODDS, LNR, and 7th and 8th pN classifications. The results (Fig. 2) showed that groups stratified by LODDS and LNR classifications had more discriminated survival rates than those stratified by the 7th and 8th pN classifications, which was consistent with the results from analyses using OS as outcome instead of CSS (Supplementary Fig. 8) and cumulative SBA death probability (Supplementary Fig. 9). The sensitivity analysis also supported the rationality of our LODDS and LNR classifications and the superiority of these classifications to those of the 7th and 8th pN based on Kaplan-Meier plots and comparison in another group of SBA patients diagnosed from 2011 to 2014 in the SEER database with similar results (Supplementary Fig. 10).

We next compared the prognostic performance of the lymph node schemes in classification patterns using similar measures; namely, R^2 value for overall performance and Harrell's C statistic for discriminatory capacity. As shown in Table 2, as measured by Harrell's C statistic, the LODDS classification (0·656; 95%CI: 0·640–0·671) still showed a better discriminatory capacity than those of the LNR (0·644; 95%CI: 0·629–0·660) and 7th pN (0·626; 95%CI: 0·611–0·642), and 8th pN (0·626; 95%CI: 0·611–0·642) classification schemes. Analyses based on AUC measures (Table 2, Supplementary Table 1 and Fig. 3) also identified the superior discriminatory capacity of the LODDS classification (five-year: 72·30%; 95%CI: 70·13%–74·46%) over those of the LNR (five-year: 70·64%; 95%CI: 68·47%–72·82%), 7th pN (five-year: 69·21%; 95%CI: 66·96%–71·46%), or 8th pN (five-year: 69·51%; 95% CI: 67·25%–71·77%) classification schemes. When the patients with systemic metastases were excluded from the cohort (Supplementary Table 4 and Supplementary Fig. 11), we could also draw the conclusion that stratified LODDS classification had a better capacity of discrimination and higher accuracy of prognosis than the pN and LNR classification with a higher R^2 (0·158), Harrell's C (0·648; 95%CI: 0·632–0·665), and five-year AUC (70·75%, 95%CI: 68·44%–73·06%) than those of pN and LNR. Meanwhile, sensitivity analyses also identified LODDS classification as the best lymph node scheme using OS instead of CSS as the outcome (Supplementary Table 1, Supplementary Table 2 and

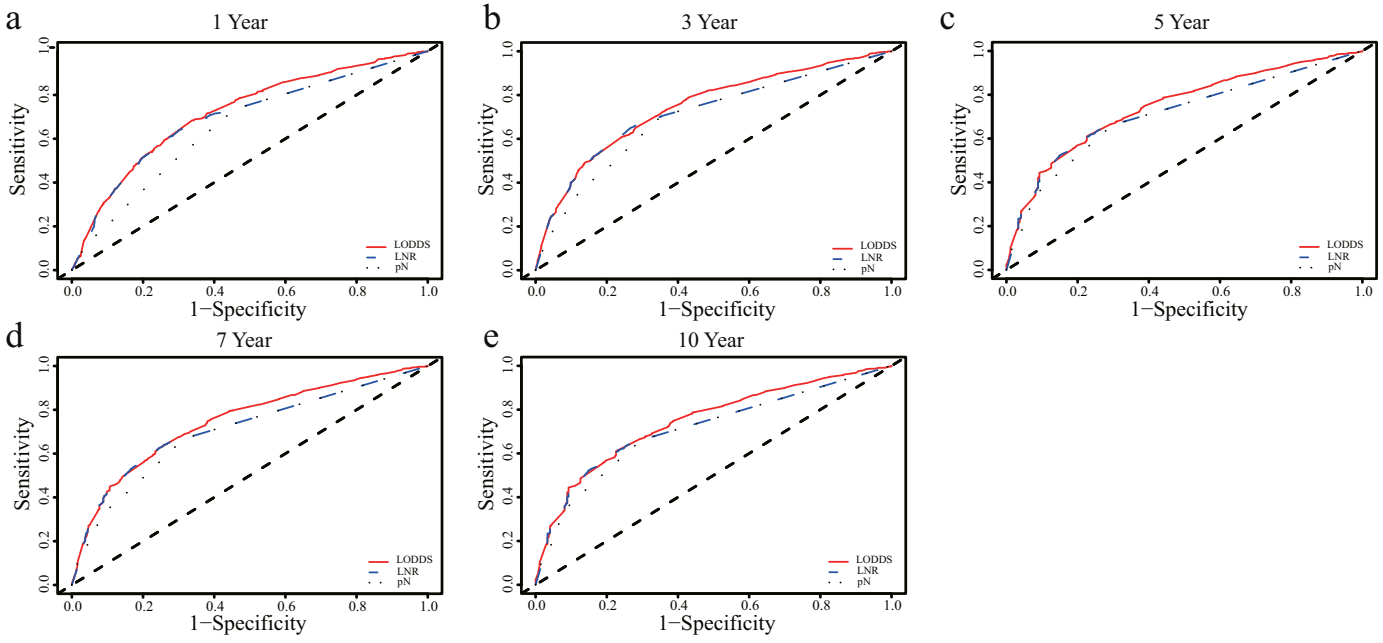

Fig. 1. ROC curve of the LODDS, LNR and pN in prediction of prognosis of patients with adenocarcinoma at 1 (a), 3 (b), 5 (c), 7 (d), 10 (e) year point for cause-specific survival in SEER database. LNR: lymph node ratio; LODDS: log odds of positive lymph nodes; pN: number of positive nodes; SEER: Surveillance, Epidemiology, and End Results.

Supplementary Fig. 12) or when the competing risk model was used in consideration of competing risk of non-SBA death (Supplementary Table 1, Supplementary Table 3 and Supplementary Fig. 13) .

The five-year survival rate for different groups decreased with increased LODDS classification for both CSS and OS (Table 3). For the 8th pN category, the five-year OS and CSS rates were 50·9% and 58·3% respectively, in N0 patients. The five-year OS and CSS rates decreased to 14·7% and 16·4%, respectively, in N2 patients. However, in the respective subgroup of pN category, the five-year CSS and OS rates were dramatically reduced with increasing LODDS classification. For instance, in N1 patients, the five-year OS rate was 48% in patients with LODDS1 and decreased to 11·4% in patients with LODDS3 disease.

The LODDS had a natural advantage in assessing patients without positive lymph node involvement. As shown in Fig. 4a, the LODDS scheme could reflect the prognosis of patients without positive lymph node involvement ($P < 0·001$).

In multivariable analysis of models with lymph node classifications in cohorts with multivariate imputation used for missing variables, the LODDS classification model had an R^2 value of 0·309, which was higher than those for the LNR (0·291) and 7th pN (0·280) and 8th pN (0·280) classifications (Table 4). In addition, the highest value of Harrell's C statistic observed in the LODDS classification model represented its superiority in discriminatory performance compared to those of the other classification schemes. Similar results were obtained in a sensitivity analysis in the group of patients without any missing clinical variables (Supplementary Table 5).

3.5. Validation of the prognostic abilities of the LODDS, LNR, and pN in a multicentre cohort

In the international multicentre cohort, the LODDS had better a R^2 value (0·131) than those of the LNR (0·110) and pN (0·049) and the LODDS (0·647; 95%CI: 0·587–0·707) also showed a better discriminatory capacity than those of the pN (0·599; 95%CI: 0·545–0·653) and LNR (0·624; 95%CI: 0·570–0·678) (Table 2).

In addition to the continuous pattern, the LODDS classification had higher R^2 (0·120) and better discriminatory capacity (0·629; 95%CI: 0·574–0·683) than those of the LNR and 7th and 8th pN classifications in the multicentre cohort (Table 2). Analyses based on AUC measures (Table 2, Supplementary Table 1, Supplementary Table 2 and Supplementary Table 3) showed that the LODDS and LODDS classification provided a better discriminatory capacity than those of the pN and LNR for CSS, OS, and competing risk model in the multicentre cohort. As shown in Supplementary Fig. 14, there appeared to be a positive correlation between LODDS or LNR and survival time. However, the correlation between LNR and survival was weak at the poles.

Fig. 5 shows that groups stratified by LODDS and LNR classifications had better discrimination than those stratified by the 7th pN and 8th pN classification schemes for CSS, consistent with the results of OS (Supplementary Fig. 15) and cumulative SBA death probability (Supplementary Fig. 16) in the multicentre cohort. For patients without positive lymph node involvement, those with LODDS2 disease had a worse outcome than those with LODDS1, a finding consistent with that in the SEER database (Fig. 4b). In multivariable analysis, the model of LODDS

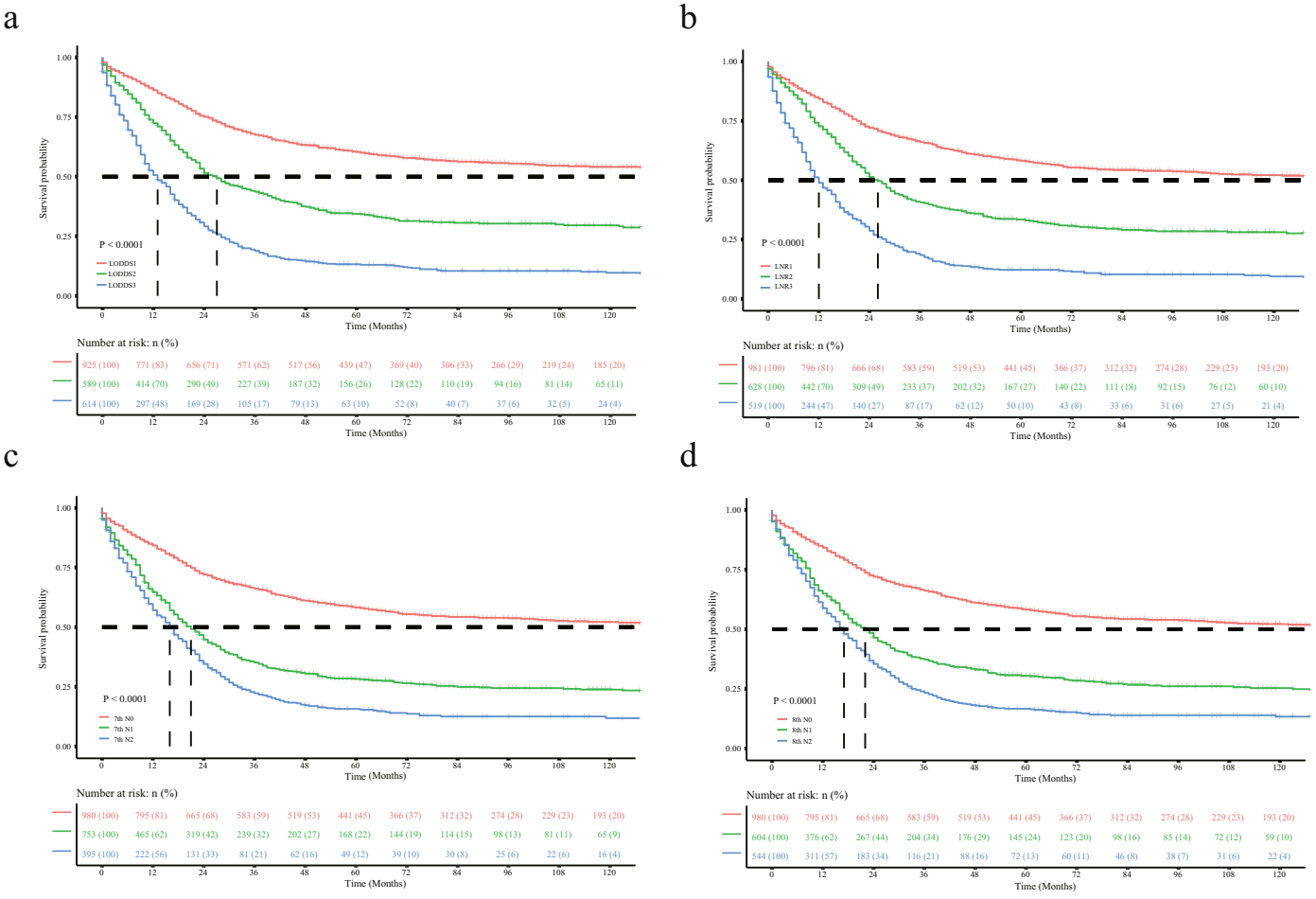

Fig. 2. Kaplan-Meier survival analysis according to LODDS classification (a) and LNR classification (b), 7th pN (c) and 8th pN(d) for cause-specific survival, respectively in SEER database. LNR: lymph node ratio; LODDS: log odds of positive lymph nodes; pN: number of positive nodes; SEER: Surveillance, Epidemiology, and End Results.

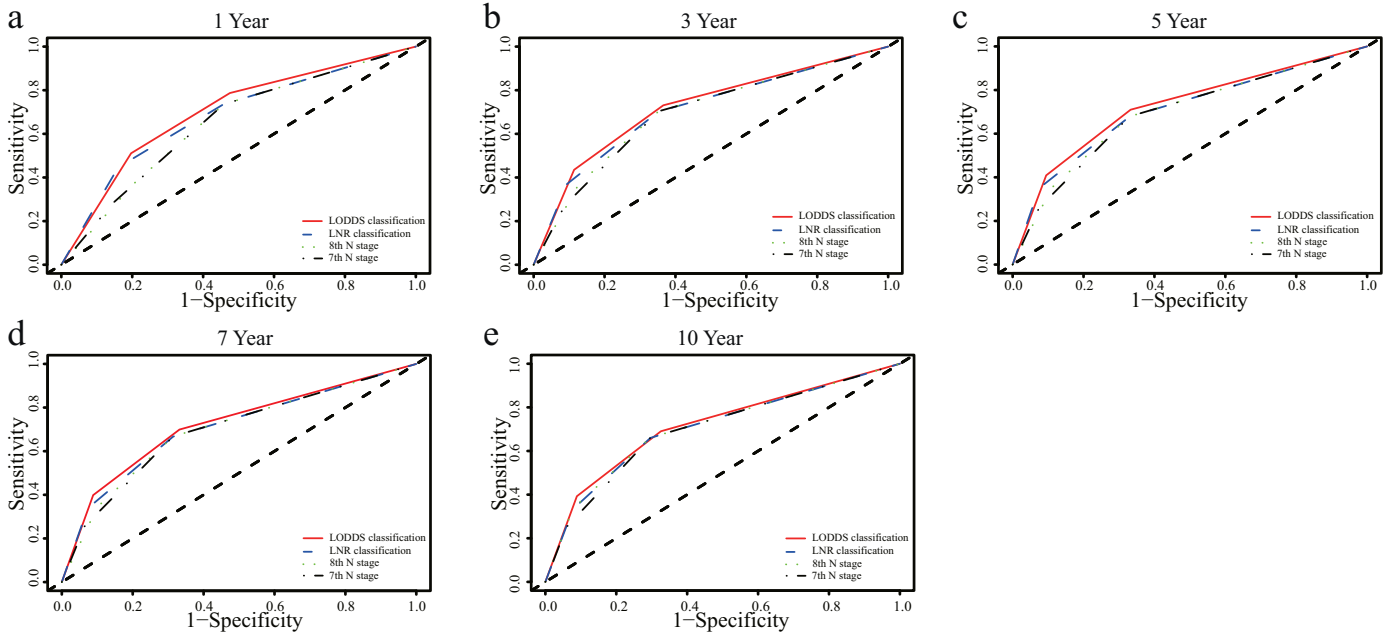

Fig. 3. ROC curve of the LODDS classification, LNR classification, 7th pN stage and 8th pN stage in prediction of prognosis of patients with adenocarcinoma at 1 (a), 3 (b), 5 (c), 7 (d), 10 (e) year point for cause-specific survival in SEER database. LNR: lymph node ratio; LODDS: log odds of positive lymph nodes; SEER: Surveillance, Epidemiology, and End Results.

Table 3
Five-Year Survival Rates for patients with small bowel adenocarcinoma stratified by LODDS and 8th pN category in SEER database.

Groups	Overall	LODDS classification			LNR classification		
		LODDS1 (≤ − 1·89)	LODDS2 (−1·89– −0·51)	LODDS3 (> − 0·51)	LNR1 (≤0·02)	LNR2 (0·02–0·47)	LNR3 (>0·47)
N0 patients							
OS (%)	50·9	55·6	31·6	NA	50·9	NA	NA
CSS (%)	58·3	62·0	42·1	NA	58·3	NA	NA
N1 patients							
OS (%)	26·4	48·0	29·6	11·4	NA	43·2	25·4
CSS (%)	30·5	53·2	33·3	13·9	NA	47·8	29·1
N2 patients							
OS (%)	14·7	NA	22·4	10·7	NA	20·0	9·8
CSS (%)	16·4	NA	24·6	12·1	NA	22·1	11·1

OS: overall survival; CSS: cause-specific survival; LODDS: log odds of positive lymph nodes; LNR: lymph node ratio; NA: Not Available.

classification also had higher R^2 and Harrell's C values than those of other classifications in the multicenter cohort (Table 4).

4. Discussion

To our knowledge, this was the largest study involving two different cohorts to compare the predictive ability of three lymph node staging schemes in the survival of patients with SBA. Our results showed that the LODDS had better prognostic evaluation and discriminatory capacities in SBA than those of the pN and LNR staging schemes for both continuous and stratified patterns. Furthermore, multivariable analysis revealed that the LODDS classification also had better predictive accuracy and discriminatory capacity than those of the 7th and 8th editions of the TNM node and LNR classification schemes. The prognostic superiority of the LODDS and LODDS classification was also validated in an international multicenter cohort using the same inclusion and exclusion criteria.

Lymph node status is a vital prognostic indicator of SBA [11,24,25]. The AJCC TNM staging currently dominates lymph node staging systems; however, the reliability of the pN staging scheme has recently been questioned. Overman et al. assessed total lymph nodes, positive lymph nodes, and LNR in 1991 patients with SBA. They found that survival after surgical resection for stage I, II, and III SBA was related to the total number of lymph nodes retrieved. In addition, among patients with stage III SBA, the LNR had prognostic performance than stratification by the number of positive lymph nodes [26]. Tran et al. evaluated the number of lymph nodes retrieved and the impact of LNR on SBA survival in the SEER database. They concluded that the total number of lymph nodes retrieved and LNR were important prognostic factors of survival in SBA and recommended that the current lymph node staging system should be updated [11].

In the present study, a median of around 6–8 lymph nodes was retrieved, with more than half of the patients with SBA lacking an adequate number of examined lymph nodes, indicating the scarcity of lymph node harvest and poor overall surgical quality [27]. SBAs are often diagnosed due to local complications such as obstruction or bleeding, leading to surgery for symptom relief but not timely recognition of oncologic resection with more lymph nodes retrieved for N staging [28,29]. This may cause poor surgery quality for SBA and a need for increased awareness. Thus, surgeons should assess lymph nodes as much as possible and surgery quality should be strongly advocated to increase the number of retrieved lymph nodes for accurate N staging. However, if surgery quality cannot be guaranteed with inadequate lymph nodes harvested, LODDS and LNR may be surrogates for pN and the LODDS scheme has better discrimination than that of LNR.

Studies have shown a positive association between an increased number of lymph nodes retrieved and a better prognosis [10,26,30,31]. To ensure the quality of surgery measured by the number of lymph nodes retrieved [27], the proposed cutoffs for the optimal number of lymph nodes varied in different studies, ranging from 8 to 15 [26,30,31]. In our previous study, we determined the optimal number of examined lymph nodes to be at least 17. In the multivariate Cox regression model, a cutoff of 17 as an adequate number of examined lymph nodes was an independent factor for better survival [10].

Since an adequate number of examined lymph nodes was associated with a better survival and was used to assess the quality of surgery, we next tried to include the adequate number of examined lymph nodes and other factors to build a predictive model for the survival of SBA patients using backward Cox analysis using Akaike information criteria

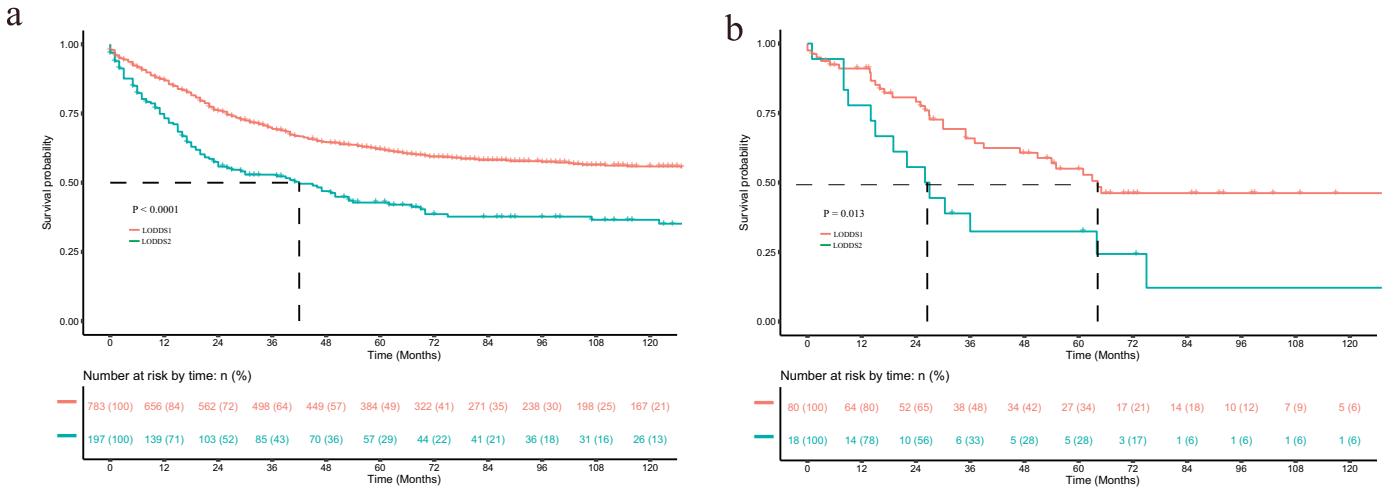

Fig. 4. Kaplan-Meier survival analysis for cause-specific survival according to LODDS classification in patients with no lymph node involvement in SEER database (a) and the international multicenter cohort (b), respectively. LODDS: log odds of positive lymph nodes.

Table 4
Multivariable analysis for prognostic performance of models with different node classifications for small intestine adenocarcinoma in SEER database with multivariate imputationused for missed variable.

Factor	LODDS classification		LNR classification		7th pN classification		8th pN classification	
	HR	P	HR	P	HR	P	HR	P
Node Stage[a]								
LODDS1/LNR1/pN0	1·00	<0·001	1·00	<0·001	1·00	<0·001	1·00	<0·001
LODDS2/LNR2/pN1	1·82 (1·58–2·11)		1·62 (1·41–1·86)		1·82 (1·59–2·08)		1·76 (1·53–2·03)	
LODDS3/LNR3/pN2	2·95 (2·55–3·40)		2·64 (2·28–3·05)		2·32 (1·99–2·71)		2·26 (1·95–2·60)	
T category[b]								
T1	1·00		1·00		1·00		1·00	
T2	1·43 (0·82–2·51)	0.204	1·40 (0·80–2·46)	0.234	1·43 (0·82–2·50)	0.206	1·44 (0·82–2·52)	0.200
T3	2·22 (1·36–3·61)	0.002	2·06 (1·26–3·38)	0.005	2·05 (1·26–3·34)	0.005	2·05 (1·26–3·33)	0.005
T4	3·11 (1·91–5·06)	<0.001	2·89 (1·77–4·74)	<0.001	2·81 (1·74–4·54)	<0.001	2·81 (1·74–4·56)	<0.001
M stage								
M0	1·00	<0·001	1·00	<0·001	1·00	<0·001	1·00	<0·001
M1	2·45 (2·14–2·81)		2·56 (2·23–2·93)		2·82 (2·47–3·26)		2·82 (2·46–3·22)	
Age								
≤ 60	1·00	<0·001	1·00	<0·001	1·00	<0·001	1·00	<0·001
>60	1·56 (1·39–1·76)		1·54 (1·37–1·73)		1·57 (1·40–1·76)		1·57 (1·39–1·76)	
Marriage								
Yes	1·00	<0·001	1·00	<0·001	1·00	<0·001	1·00	<0·001
No	1·22 (1·09–1·38)		1·23 (1·09–1·39)		1·25 (1·11–1·41)		1·25 (1·11–1·41)	
Sex								
Male	1·00	0·024	1·00	0·032	1·00	0·007	1·00	0·006
Female	0·87 (0·78–0·98)		0·88 (0·78–0·99)		0·85 (0·76–0·96)		0·85 (0·75–0·95)	
Grade								
I/II	1·00	<0·001	1·00	<0·001	1·00	<0·001	1·00	<0·001
III/IV	1·30 (1·16–1·46)		1·31 (1·17–1·47)		1·28 (1·14–1·44)		1·27 (1·14–1·43)	
Site								
Duodenum	1·00		1·00		1·00		1·00	
Ileum	0·92 (0·78–1·07)	0·283	0·91 (0·78–1·07)	0·244	0·87 (0·74–1·01)	0·075	0·87 (0·75–1·02)	0·087
Jejunum	0·76 (0·66–0·88)	<0·001	0·78 (0·68–0·91)	0·001	0·78 (0·67–0·90)	0·009	0·77 (0·67–0·89)	0·009
Others[c]	0·99 (0·66–1·50)	0·963	1·05 (0·69–1·59)	0·832	1·04 (0·67–1·61)	0·877	1·04 (0·67–1·61)	0·870
Model performance[d]								
SEER database								
Mean R^2	0·309		0·291		0·280		0·280	
Mean with range of Harrell's C	0·730 (0·708–0·742)		0·723 (0·701–0·745)		0·717 (0·695–0·739)		0·717 (0·695–0·739)	
Multicenter cohort								
R^2	0·191		0·155		0·142		0·140	
Harrell's C	0·663 (0·602–0·724)		0·654 (0·593–0·715)		0·642 (0·581–0·703)		0·649 (0·588–0·710)	

LNR: lymph node ratio; LODDS: log odds of positive lymph nodes; pN: number of positive nodes.
[a] Represent the 7thpN, 8thpN, LODDS classifications and LNR classifications for corresponding multivariable models.
[b] Tumor category were graded according to the 8thtumour node metastasis (TNM) classification of malignant tumors proposed by the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC), whereas M stage was recorded metastatic disease pathologically coded 85 in extent of disease "EOD 10-extent (1988–2003)" of Surveillance, Epidemiology, and End Results (SEER) data.
[c] Others were recorded because tumors were located in the Meckels diverticulum or overlapping lesion of small intestine.
[d] Indicates the joint prognostic performance of models with different node staging schemes.

(AIC) selection criteria [10]. However, the factor was excluded from the predictive model since the model that included the factor did not have the lowest AIC. The number of examined lymph nodes should be considered since nearly half of cancers did not meet this criterion. Hence, we assessed the performance of the three lymph node schemes most commonly used to determine prognosis, namely, the pN, LNR, and LODDS schemes.

It stands to reason that the LODDS is better than the pN and LNR staging schemes. The pN staging scheme only records the absolute number of positive lymph nodes without considering the numbers of total and negative lymph nodes retrieved. Visually, both LODDS and LNR are more rational than the pN staging scheme for consideration of the number of positive or negative and total lymph nodes. Some researchers have questioned the prognostic accuracy of LNR [32,33], especially when all or no retrieved lymph nodes are metastatic.

As shown in Supplementary Fig. 7 and Supplementary Fig. 14, patients with the same LNR may have different outcomes. For example, the LNR may be the same for patients with one metastatic node out of one retrieved as for forty metastatic nodes out of forty retrieved, which is a fatal drawback of the LNR scheme. In contrast, the LODDS can further stratify patients with no (Fig. 4) or all metastatic nodes retrieved. Close analysis of the data in Table 3 revealed that some patients with N0 disease had worse survival than those with N1 and that some patients with N1 disease had a poorer prognosis than those with N2, which could be shown by LODDS instead of LNR classification. According to the definition of LNR, almost all of the N0 patients belonged to the subgroup of LNR1 and most of the N1 and N2 patients were LNR2 and LNR3. In any LNR subgroup, the five-year OS and CSS rates decreased with increasing pN category, in contrast to the LODDS classification, which indicated the flaws of pN category in evaluating OS and CSS of patients with SBA. The LODDS classification had greater power of discrimination compared to that of the LNR scheme.

We found that the OS and CSS of duodenal carcinoma were worse than those of jejunoileal tumors when we assessed the five-year survival rate and number of retrieved lymph nodes from different locations (Supplementary Table 6), consistent with the findings of a previous study [26]. Comparison of the number of retrieved lymph nodes between the duodenum and jejunum or between the ileum and jejunum revealed that the OS and CSS improved with more lymph nodes being assessed. However, the finding was contrary to the survival rate of carcinoma located in the duodenum and ileum; one explanation for this phenomenon may be that the number of examined lymph nodes is not the only factor affecting the outcome and other risk factors such as different pathogenesis could also contribute to the outcome [26].

This study has some limitations. First, the retrospective study design had an inherent bias. The predictive performance of lymph node staging

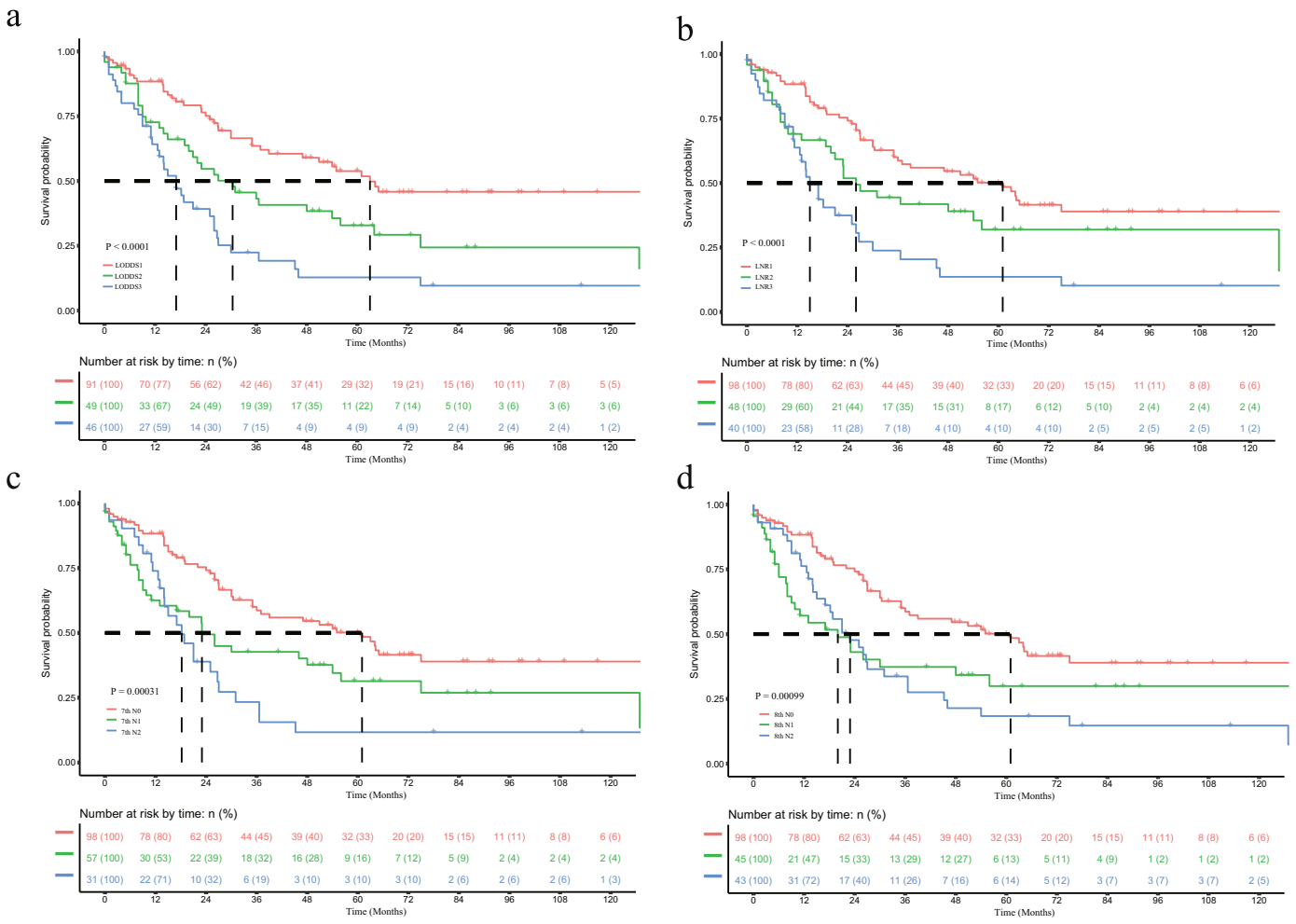

Fig. 5. Kaplan-Meier survival analysis according to LODDS classification (a) and LNR classification (b), 7th pN (c) and 8th pN (d) for cause-specific survival in the international multicentre cohort, respectively. LNR: lymph node ratio; LODDS: log odds of positive lymph nodes; pN: number of positive nodes.

schemes cannot be completely illuminated without a prospective and randomized clinical trial. The SEER database lacked information on adjuvant therapy, genetic status, etc. [2,34,35], which may be confounding factors for prognosis. However, the sample capacity of this study, which we believed to be sufficient, and the long duration of follow up could make up for these drawbacks and provide a comprehensive view of the prognostic ability of three common lymph node staging schemes in SBA. We found a superior prognostic ability of the LODDS in patients with SBA in the SEER database and uniquely verified our finding in a cohort from Europe and Asia. The approaches were methodologically sound and the results were statistically compelling and convincing.

5. Conclusion

In conclusion, LODDS scheme showed a better prognostic ability than pN or LNR scheme in patients with SBA. LODDS could serve as a significant auxiliary of lymph node staging system in the future revisions of the AJCC manual and surgical guidelines to improve prediction for prognosis of SBA.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2019.02.043.

Acknowledgements

The authors harbor sincere gratitude for the efforts of the SEER program in the establishment of the SEER database. Patients were included from the following mentioned hospitals:Ambroise Paré (Boulogne), Georges Pompidou (Paris), Saint Antoine (Paris), Rouen universitary hospital (Rouen), Saint Louis (Paris), Henri Mondor (Créteil), Institut Gustave Roussy (Villejuif), Bichat (Paris), Tours universitary hospital (Tours), Kremlin-Bicêtre (Kremlin-Bicêtre), Meaux hospital (Meaux) and Pitié-Salpétrière (Paris) from France, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical UniversityWenzhou (Zhejiang), The First Affiliated Hospital of Wenzhou Medical University (Zhejiang) and Shanghai Ninth People's Hospital (Shanghai) from China.

Funding sources

This work was supported by Zhejiang Province Natural Science Fund of China (grant number LY14H030001).

Declarations of interests

The authors declare no potential conflicts of interest

Author contributions

Literature search and study design: Y. Zhou, Q. Zhang and H. Wang. Data analysis: Y. Zhou, Q. Zhang and C. Zhang. Data collection From France: T. Aparicio, A. Zaanan and P. Afchain. Data collection From China: L. Chen and C. Zhang. Figure processing: X. Du and S. Hu. Manuscript writing: Y. Zhou and P. Zhang. Suggestion: M. Wu.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
[2] Raghav K, Overman MJ. Small bowel adenocarcinomas—existing evidence and evolving paradigms. Nat Rev Clin Oncol 2013;10:534–44.
[3] Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg 2009;249:63–71.
[4] Pan SY, Morrison H. Epidemiology of cancer of the small intestine. World J Gastrointest Oncol 2011;3:33–42.
[5] Howe JR, Karnell LH, Menck HR, Scott-Conner C. The American college of surgeons commission on cancer and the American cancer society. Adenocarcinoma of the small bowel: review of the national cancer data base, 1985−1995. Cancer 1999; 86:2693–706.
[6] Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg 2010;199: 797–803.
[7] de Bree E, Rovers KP, Stamatiou D, Souglakos J, Michelakis D, de Hingh IH. The evolving management of small bowel adenocarcinoma. Acta Oncol 2018 Jun;57(6): 712–22.
[8] Chang HK, Yu E, Kim J, et al. Adenocarcinoma of the small intestine: a multi-institutional study of 197 surgically resected cases. Hum Pathol 2010;41:1087–96.
[9] Gu MJ, Kim JY, Park JB. Fascin expression predicts lymph node metastasis and worse survival in small intestinal carcinoma. Pathology 2014;46:21–4.
[10] Wu S, Chen JN, Zhang QW, et al. A new metastatic lymph node classification-based survival predicting model in patients with small bowel adenocarcinoma: a derivation and validation study. EBioMedicine 2018;32:134–41.
[11] Tran TB, Qadan M, Dua MM, Norton JA, Poultsides GA, Visser BC. Prognostic relevance of lymph node ratio and total lymph node count for small bowel adenocarcinoma. Surgery 2015;158:486–93.
[12] Scarinci A, Di Cesare T, Cavaniglia D, et al. The impact of log odds of positive lymph nodes (LODDS) in colon and rectal cancer patient stratification: a single-center analysis of 323 patients. Updates Surg 2018;70:23–31.
[13] Aurello P, Petrucciani N, Nigri GR, et al. Log odds of positive lymph nodes (LODDS): what are their role in the prognostic assessment of gastric adenocarcinoma? J Gastrointest Surg 2014;18:1254–60.
[14] Dziedzic D, Piotr R, Langfort R, Orlowski T, Polish Lung Cancer Study Group (PLCSG). Log odds of positive lymph nodes as a novel prognostic indicator in NSCLC staging. Surg Oncol 2017;26:80–5.
[15] Chen LJ, Chung KP, Chang YJ, Chang YJ. Ratio and log odds of positive lymph nodes in breast cancer patients with mastectomy. Surg Oncol 2015;24:239–47.
[16] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK. AJCC cancer staging manual. Springer; 2017.
[17] La Torre M, Nigri G, Petrucciani N, et al. Prognostic assessment of different lymph node staging methods for pancreatic cancer with R0 resection: pN staging, lymph node ratio,log odds of positive lymph nodes. Pancreatology 2014;14:289–94.
[18] Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res 2004;10:7252–9.
[19] Schemper M. Predictive accuracy and explained variation. Stat Med 2003;22: 2299–308.
[20] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
[21] Smith PJ, Hoaglin DC, Battaglia MP, Barker L. Implementation and applications of bootstrap methods for the national immunization Survey. Stat Med 2003;22: 2487–502.
[22] Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Stat Med 2013;32:5381–97.
[23] van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1–67.
[24] Wu TJ, Yeh CN, Chao TC, Jan YY, Chen MF. Prognostic factors of primary small bowel adenocarcinoma: univariate and multivariate analysis. World J Surg 2006;30:391–8.
[25] Aparicio T, Zaanan A, Svrcek M, et al. Small bowel adenocarcinoma: epidemiology, risk factors, diagnosis and treatment. Dig Liver Dis 2014;46:97–104.
[26] Overman MJ, Hu CY, Wolff RA, Chang GJ. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. Cancer 2010;116:5374–82.
[27] Wong SL, Ji H, Hollenbeck BK, Morris AM, Baser O, Birkmeyer JD. Hospital lymph node examination rates and survival after resection for colon cancer. JAMA 2007; 298:2149–54.
[28] Negoi I, Paun S, Hostiuc S, et al. Most small bowel cancers are revealed by a complication. Einstein 2015;13:500–5.
[29] Brophy C, Cahow CE. Primary small bowel malignant tumors. Unrecognized until emergent laparotomy. Am Surg 1989;55:408–12.
[30] Nicholl MB, Ahuja V, Conway WC, Vu VD, Sim MS, Singh G. Small bowel adenocarcinoma: understaged and undertreated? Ann Surg Oncol 2010;17:2728–32.
[31] Ecker BL, McMillan MT, Datta J, et al. Lymph node evaluation and survival after curative-intent resection of duodenal adenocarcinoma: a matched cohort study. Eur J Cancer 2016;69:135–41.
[32] Huang B, Ni M, Chen C, Cai G, Cai S. LODDS is superior to lymph node ratio for the prognosis of node-positive rectal cancer patients treated with preoperative radiotherapy. Tumori 2017;103:87–92.
[33] Ramacciato G, Nigri G, Petrucciani N, et al. Prognostic role of nodal ratio, LODDS, pN in patients with pancreatic cancer with venous involvement. BMC Surg 2017;17: 109.
[34] Nakanoko T, Koga T, Taketani K, et al. Characteristics and treatment strategies for small bowel adenocarcinoma in advanced-stage cases. Anticancer Res 2015;35: 4135–8.
[35] Laforest A, Aparicio T, Zaanan A, et al. ERBB2 gene as a potential therapeutic target in small bowel adenocarcinoma. Eur J Cancer 2014;50:1740–6.