



Research paper

Personalized four-category staging for predicting prognosis in patients with small bowel Adenocarcinoma: an international development and validation study



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ABSTRACT

Background: Log odds of positive lymph nodes (LODDS) classification showed superiority over 8th edition N staging in predicting survival of small bowel adenocarcinoma (SBA) patients. The aim of this study was to develop and validate the Tumor, LODDS, and Metastasis (TLM) staging of SBA.

Methods: Totally 1789 SBA patients from the Surveillance, Epidemiology, and End Results (SEER) database between 1988–2010, 437 patients from SEER database between 2011–2013 and 166 patients from multi-centers were categorized into development, validation and test cohort, respectively. The TLM staging was developed in the development cohort using Ensemble Algorithm for Clustering Cancer Data (EACCD) method. C-index was used to assess the performance of the TLM staging in predicting cancer-specific survival (CSS) and was compared with the traditional 8th edition TNM staging.

Findings: Four-category TLM staging designed for the development cohort showed higher discriminatory power than TNM staging in predicting CSS in the development cohort (0.682 vs. 0.650, $P < 0.001$), validation cohort (0.682 vs. 0.654, $P = 0.022$), and test cohort (0.659 vs. 0.611, $P = 0.023$), respectively. TLM staging continued to show its higher predictive efficacy than the 8th TNM in TNM stage II/III patients or in patients with lymph node yield less than 8.

Interpretation: TLM staging showed a better prognostic performance than the 8th TNM staging especially TNM stage II/III or patients with lymph node yield less than 8 and therefore, could serve to complement the TNM staging in patients with SBA.

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1. Introduction

Although small bowel cancers are rare cancers of digestive system, comprising < 5% of gastrointestinal tumors [1,2], incidence of small bowel adenocarcinoma (SBA), the most common histology of small bowel tumors, is on the rise [2,3]. However, predicting prognosis of SBA has been difficult due to controversial results shown by the

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Research in Context section

Evidence before this study

We performed literature search for the treatment and survival of small bowel adenocarcinoma (SBA) and evaluation of lymph node metastasis and TNM staging in patients with SBA, particularly in PubMed with the keyword “small bowel adenocarcinoma”. We found that lymph node metastasis and TNM stage is considered one of the most robust prognostic markers for SBA using multivariate analysis. However, the role of the number of positive lymph nodes, lymph node ratio and log odds of positive lymph nodes in SBA are ill-defined. Furthermore, we found that there are ongoing studies to identify a novel staging to complement TNM stage since a large percent of patients undergo lymph node yield less than 8.

Added value of this study

This study was conducted in three independent cohorts to establish and validate a novel staging, named the TLM staging for Tumor, Log odds of positive lymph nodes (LODDS), and Metastasis (TLM) staging. We evaluated SBA patients diagnosed between 1988–2010 from the Surveillance, Epidemiology, and End Results database (SEER), and found a superior prognostic predictive ability of the TLM staging compared to the TNM staging. We validated the findings by evaluating SBA patients diagnosed between 2011–2013 from SEER database and also the patients from an international cohort of patients from France and China. Furthermore, TLM staging continued to show its higher predictive efficacy than the 8th TNM in patients with TNM stage II/III or in patients with lymph node yield less than 8.

Implications of all the available evidence

TLM staging showed a better prognostic performance than TNM staging especially TNM stage II/III or in patients with lymph node yield less than 8. Since a high percent of SBA patients do not have low lymph node yield due to need for emergent surgery for symptom relief, TLM staging could improve predictive power of SBA prognosis and provide surgical guidelines in revised version of the American Joint Committee on Cancer (AJCC) manual.

2. Methods

2.1. Patients

To develop the novel TLM staging system, we used the SEER database to retrieve patients diagnosed with SBA between 1988 to 2010 for the development cohort. The patients were chosen based on our previously published criteria [8], which were as follows: patients (1) with histologically-confirmed SBA; (2) older than 18 years of age; (3) treated with surgery; (4) not receiving radiotherapy for the first round of therapy; (5) close follow-up with available survival outcome; (6) had at least one lymph node histologically examined; (7) had information about T and M stage available.

Data of patients with SBA during 2011–2013 with at least 3 years follow-up were obtained from the SEER database for the validation cohort for the novel TLM stage using the same inclusion criteria. Another independent international multicenter cohort of 166 patients with SBA from Ambroise Paré (Boulogne), Georges Pompidou (Paris), Saint Antoine (Paris), Rouen university hospital (Rouen), Saint Louis (Paris), Henri Mondor (Créteil), Institut Gustave Roussy (Villejuif), Bichat (Paris), Tours university hospital (Tours), Kremlin-Bicêtre (Kremlin-Bicêtre), Meaux hospital (Meaux) and Pitié-Salpêtrière (Paris) in France, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Zhejiang), Shanghai Tenth People's Hospital (Shanghai) and Shanghai Ninth People's Hospital (Shanghai) in China from 1998–2013 according to the same inclusion criteria was used as the test cohort for our novel TLM stage. The study protocol was approved by all participating hospitals. Informed consent was obtained from each patient before surgery.

2.2. Definitions of outcome and TLM stage

In the study, cancer-specific survival (CSS), overall survival (OS) and recurrence-free survival (RFS) were the measured outcomes. CSS was defined as survival without death caused by SBA and OS was defined as survival without death regardless of any causes. RFS was defined as survival without recurrence of primary SBA. LODDS was defined as $\log_e[(Pn + 0.5)/(nN + 0.5)]$ [8], where pN is the number of positive LNs and nN is the number of negative LNs. Based on our previous study [8], LODDS is classified into three categories: LODDS1 (LODDS ≤ -1.89), LODDS2 (LODDS > -1.89 and LODDS ≤ -0.51) and LODDS3 (LODDS > -0.51). T stage and M stage were defined according to the AJCC 8th edition TNM staging. In this study, the novel TLM staging was defined according to four stages that combined T stages, LODDS stages and M stages (Supplementary Table 1).

2.3. Statistical analysis

Statistical analysis was performed using R software (version 3.0.1; <http://www.Rproject.org>). For descriptive statistics, the absolute number with proportion was used as categorical variables. The chi-square test was then used to compare categorical variables among different groups. For survival analysis, Kaplan-Meier method was used to calculate and compare survival rates among different patient groups, with log-rank test used for statistical comparisons. The reported statistical significance levels were all two-sided, with statistical significance set at 0.05.

2.4. Development of the novel TLM stage

In this study, the EACCD, a machine learning algorithm designed to partition survival data, was used to develop the TLM stage [9,10]. This algorithm was performed in three steps. [1] Initial dissimilarities between survival functions of any two combinations is calculated and log-rank test is employed to test whether a difference exists in

tumor, lymph node and metastasis staging (TNM) and the number of retrieved lymph nodes (LNs) staging systems [4,5].

In order to find the optimal number of examined LNs needed for accurate LN staging and predicting survival, K-adaptive partitioning (KAPS) algorithm was used, which was described previously [6]. Using this method, we were able to obtain heterogeneous subgroups by survival and optimal cut-off points were found by evaluating potential multi-splits. Using a statistical method, seventeen was identified as the minimal number of retrieved LNs needed for TNM staging. However, more than 80% of SBAs did not have adequate LN histological examination for accurate TNM staging [7].

To find an easy-to-use and accurate measure for LN staging of the retrieved LNs, we compared three LN staging schemes. Log odds of positive lymph nodes (LODDS) was identified as the most accurate measure in predicting SBA survival [8]. Meanwhile, LODDS was classified into three-category and validated its utility in predicting survival in an international multicenter cohort [8]. Based on the results from our previous studies, a novel staging system was developed, called TLM staging, using data from population-based Surveillance, Epidemiology, and End Results (SEER) database. We then tested and validated the utility of the developed TLM staging and compared it with traditional 8th edition TNM staging in independent cohorts.

survival between two survival functions associated with the two combinations. [2] Learned dissimilarities is obtained by two-phase Partitioning Around Medoids algorithm [11] based on initial dissimilarities, an ensemble learning process, to measure the difference between two survival functions associated with two clusters of combinations. [3] Combinations are clustered by applying hierarchical clustering analysis of learned dissimilarities. In this study, the complete linkage method is chosen for hierarchical clustering [12]. To avoid bias due to small size, only combination with at least 10 patients were selected for EACCD training.

After application of EACCD in the development cohort, C-index, a measure estimating the probability that a subject who experienced an event in an earlier time had a shorter predicted time than a subject who experienced the event in a later time, was used to cut dendrograms [13]. A higher C-index indicates a higher accuracy of the developed model in prediction of prognosis. Generally, the curve of the C-index versus the number of groups increases for initially small numbers of groups with a quick plateau as more groups are generated. The optimal number of groups could be found for the model using by finding the “knee” point of the curve, which balances the simplicity and the accuracy of the system.

2.5. Performance of the TLM stage with comparison with the 8th TNM stage

The prognostic performances of the novel TLM staging and the 8th edition TNM stage were compared with CSS and OS as outcomes, respectively. Overall model performance was evaluated by R², which demonstrated that the extent of survival variability could be explained by a predictive model [14]. High R² value indicated superiority of the prognostic model. Regarding the discriminatory power, C-index was used to evaluate the proportion of positive predictive value for a predictive model [15]. Z score test was used to compare C-index of the TLM stage with that of the 8th edition TNM staging for CSS and OS [16]. In addition, bias-corrected C-index was calculated using bootstrap method (N = 1000) [17].

To further analyze and compare prognostic performances under competing risk model for CSS, adjusted C-index and bootstrapped (N = 1000) corrected C-index in consideration of competing risk was also calculated for the TLM staging and the 8th edition TNM staging [18].

Similarly, c-index and R² for the novel TLM staging were also calculated for the validation cohort and the test cohort and were compared with the 8th edition TNM staging. Z score test also was used to compare C-index of the TLM staging with that of the 8th TNM staging for CSS, OS and RFS [16].

2.6. Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had decision-making responsibility to submit the study for publication.

3. Results

3.1. Clinical characteristics

Clinical characteristics of the patients with SBA in the development, the validation, and the test cohort are given in Table 1. As is shown in Table 1, There were no significant differences among the patients in the three cohorts based on sex (P = 0.113), age (P = 0.058) and tumor grade (P = 0.387). However, there were significant differences in LODDS stage (P = 0.042), T stage (P = 0.002), M stage (P = 0.006) and N stage (P = 0.021), which incorporated both the novel TLM and 8th edition TNM staging, reflecting real world practice.

Table 1

Clinical characteristics of different patient cohort with small bowel adenocarcinoma

	Development cohort N = 1789	Validation cohort N = 437	Test cohort N = 166	P
Sex				0.113
Male	928(0.5187)	243(0.5561)	77(0.4639)	
Female	861(0.4813)	194(0.4439)	89(0.5361)	
Age (years)				0.058
<= 60	751(0.4198)	161(0.3684)	77(0.4639)	
> 60	1038(0.5802)	276(0.6316)	89(0.5361)	
Tumor site				<0.001
Duodenum	821(0.4589)	224(0.5126)	115(0.6928)	
Ileum	419(0.2342)	110(0.2517)	20(0.1205)	
Jejunum	549(0.3069)	103(0.2357)	31(0.1867)	
Grade				0.387
I/II	1095(0.6121)	275(0.6293)	110(0.6627)	
III/IV	694(0.3879)	162(0.3707)	56(0.3373)	
8 th T stage				0.002
T1	86(0.0481)	21(0.0481)	4(0.0241)	
T2	113(0.0632)	34(0.0778)	22(0.1325)	
T3	861(0.4813)	176(0.4027)	73(0.4398)	
T4	729(0.4075)	206(0.4714)	67(0.4036)	
8 th M stage				0.006
M0	1594(0.891)	365(0.8352)	145(0.8735)	
M1	195(0.109)	72(0.1648)	21(0.1265)	
8 th N stage				0.021
N0	862(0.4818)	197(0.4508)	89(0.5361)	
N1	483(0.27)	101(0.2311)	38(0.2289)	
N2	444(0.2482)	139(0.3181)	39(0.2349)	
LODDS stage ¹				0.042
LODDS1	841(0.4701)	217(0.4966)	82(0.494)	
LODDS2	489(0.2733)	138(0.3158)	44(0.2651)	
LODDS3	459(0.2566)	82(0.1876)	40(0.241)	

LODDS: log odds of positive lymph nodes.

1. LODDS stage was defined and validated in our previous published article (see reference [8]).

3.2. Development and validation for TLM stage

The four categories for the novel TLM stage were established in the development cohort using the EACCD algorithm (Fig. 1A and Fig. 1B). To demonstrate established TLM staging better, an easier readable figure is shown in Fig. 1C. As can be seen, the number of patients in some combinations was too small to classify into corresponding categories, which lead to some unclassified combinations. In the development cohort, only 9 (0.5%) patients were unclassified. To demonstration the novel TLM staging better, the unclassified combinations was reclassified according to the principle of developed TLM staging (Fig. 1D).

According to the novel TLM staging shown in the Table 2, the 3-year survival rate of TLM stage I, II, III, and IV were 77.1%, 57.1%, 35.1% and 17.2%, respectively for CSS (Fig. 2A, P < 0.001). For The development cohort, the 3-year survival rate of the four TLM stages were 71.4%, 51.4%, 31.5% and 15.1% for OS (Fig. 2B, P < 0.001) respectively. The cumulative incidence of SBA-associated death is shown in the Fig. 2C (P < 0.001). As shown in Table 3, TLM staging system had higher C-index (0.682 vs. 0.650, P < 0.001) and higher R² (0.216 vs. 0.160) than the 8th edition TNM staging system (Fig. 3A, P < 0.001) in predicting CSS of SBA patients. Similar results were obtained when comparing the TLM staging and the 8th edition TNM staging (Fig. 3B and Fig. 3C, P < 0.001) with OS (P < 0.001) and CSS under competing risk as outcome, respectively.

In the validation cohort, only 4 patients (0.9%) were unclassified. As shown in Table 2, three-year survival rate of TLM stage I, II, III, and IV was 77.2%, 63.1%, 37.9% and 21.2%, respectively for CSS (Fig. 2D, P < 0.001) and 72.0%, 56.3%, 36.8% and 19.3%, respectively for OS (Fig. 2E, P < 0.001) stratified by the TLM staging. Cumulative incidence of SBA death is shown in the Fig. 2F (P < 0.001). Compared with the 8th edition TNM staging (Fig. 3D, P < 0.001), TLM staging showed higher accuracy in predicting CSS of the patients with SBA, as

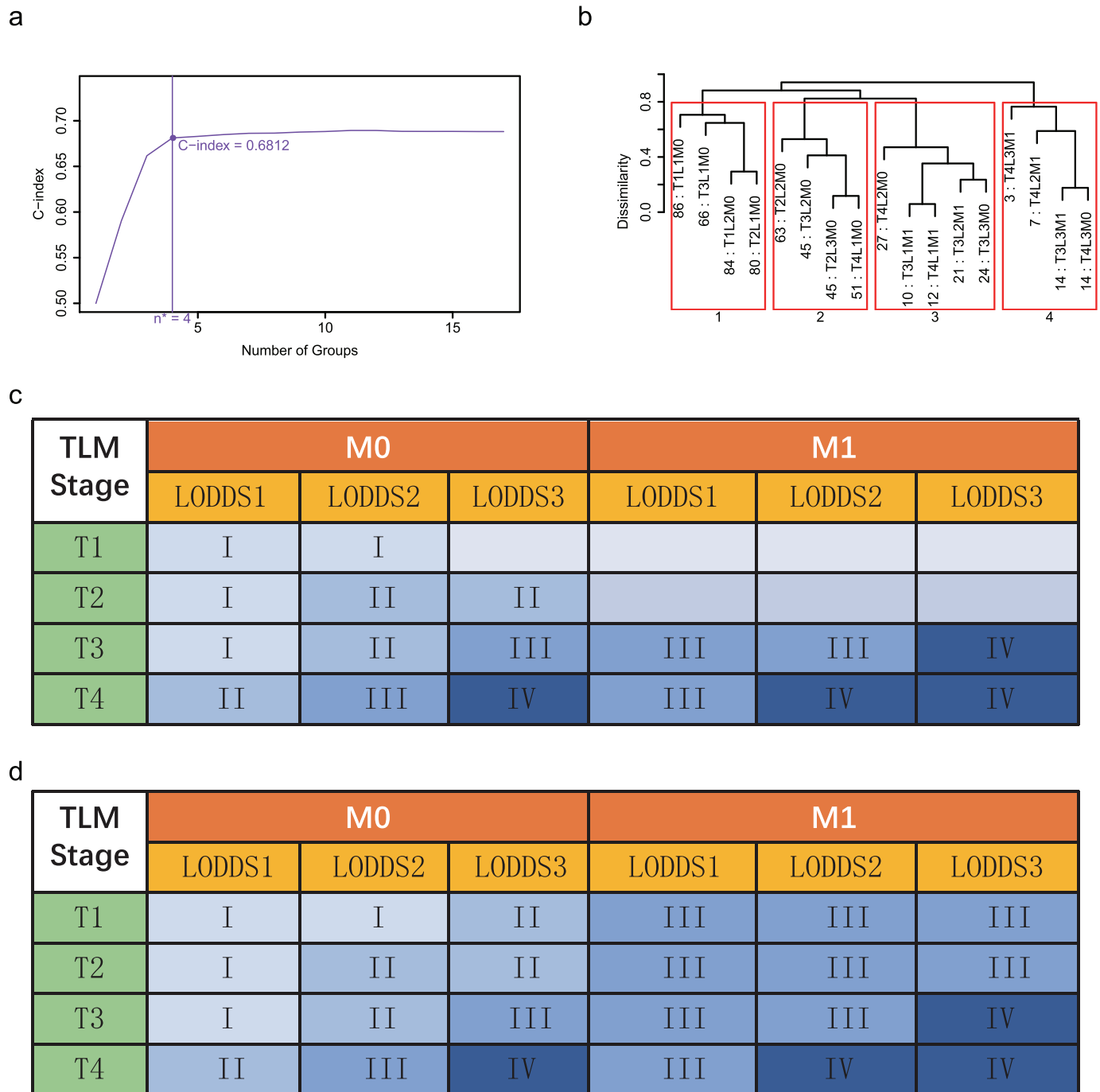


Fig. 1. Development of the novel TLM staging. (A) Curve of C-index based on the dendrogram in (B). The number 0.6812 is the C-index corresponding to $n = 4$ prognostic groups. (B) Dendrogram (in black) for the development cohort. A 5-year survival rate is given beneath each combination. Cutting the dendrogram according to $n = 4$ in (A) creates 4 prognostic groups, shown in red square boxes. Listed on the bottom are the group numbers. (C) The novel TLM staging plotted according to the tree-structured dendrogram with unclassified combinations for T, LODDS and M classification. (D) The novel TLM stage plotted according to the tree-structured dendrogram after imputation for missing stages due to unclassified combinations.

measured by C-index (0.682 vs. 0.654, $P = 0.022$) and R^2 (0.195 vs. 0.163). As shown in Table 3, similar results could be obtained when comparing the TLM staging and the 8th TNM staging (Fig. 3E and Fig. 3F, $P = 0.001$) with OS (0.654 vs. 0.622, $P < 0.001$) and CSS under competing risk (0.685 vs. 0.658) as outcomes, respectively.

3.3. Test for TLM stage

An international cohort consisting of 166 patients from 15 hospitals was used to test whether the TLM staging maintained higher

accuracy in predicting survival of patients with SBA compared with the 8th TNM staging. In the test cohort, all patients were classified into corresponding category. As shown in Table 2, 3-year survival rate of stage I, II, III, and IV were 72.2%, 66.1%, 50.5% and 22.7%, respectively for CSS (Fig. 2G, $P < 0.001$), 65.3%, 61.3%, 48.3% and 17.0%, respectively for OS (Fig. 2H, $P < 0.001$) and 67.2%, 53.4%, 31.5% and 10.2%, respectively for RFS (Fig. 2I, $P < 0.001$) stratified by the TLM stage. Cumulative incidence of SBA death is shown in the Fig. 2J ($P < 0.001$).

With respect to the TNM staging, 3-year survival rate of stage I, II, III, and IV were 67.7%, 64.0%, 56.1% and 28.6%, respectively for CSS

Table 2
Three-year survival rate for patients with small bowel adenocarcinoma according to TLM staging and TNM staging in different cohorts.

	TLM Stage											
	Development cohort				Validation cohort				Test cohort			
	I	II	III	IV	I	II	III	IV	I	II	III	IV
TNM Stage												
CSS												
Overall	77.1%	57.1%	35.1%	17.2%	77.2%	63.1%	37.9%	21.2%	72.2%	66.1%	50.5%	22.7%
I	85.8%	78.7%			78.0%				70.2%			
II	76.0%	58.5%	46.8%		79.8%	62.1%			67.2%	60.5%		
III	66.6%	53.2%	33.5%	21.6%	71.8%	61.9%	42.1%	32.4%		67.7%	45.9%	32.4%
IV			31.9%	11.7%			26.1%	11.9%			55.6%	16.7%
OS												
Overall	71.4%	51.4%	31.5%	15.1%	72.0%	56.3%	36.8%	19.3%	65.3%	61.3%	48.3%	17.0%
I	76.6%	64.9%			66.3%				70.2%			
II	70.9%	52.2%	43.5%		78.5%	50.6%			59.1%	49.6%		
III	63.4%	48.9%	29.9%	18.1%	69.6%	59.6%	41.3%	31.0%		67.7%	45.9%	32.4%
IV			30.1%	10.9%			26.1%	9.5%			55.6%	16.7%
RFS												
Overall									67.2%	53.4%	31.5%	10.2%
I									77.4%			
II									59.5%	45.7%		
III										58.2%	31.1%	13.0%
IV											44.4%	8.3%

TLM: tumor, log odds of positive lymph nodes and metastasis; TNM: tumor, log odds of positive lymph nodes and metastasis; CSS: cancer-specific survival; OS: overall survival; RFS: recurrence-free survival

(Fig. 3G, $P < 0.001$), 64.5%, 55.7%, 54.7% and 28.6%, respectively for OS (Fig. 3H, $P < 0.001$) and 74.6%, 50.4%, 40.5% and 16.7%, respectively for RFS (Fig. 3I, $P < 0.001$) stratified by the 8th edition TNM staging. Cumulative incidence of SBA death is shown in the Fig. 3J ($P < 0.001$).

As shown in Table 3, TLM staging demonstrated higher accuracy in predicting CSS (C-index: 0.659 vs. 0.611, $P = 0.023$; R^2 : 0.141 vs. 0.102), OS (C-index: 0.624 vs. 0.580, $P = 0.001$; R^2 : 0.108 vs. 0.08), RFS (C-index: 0.653 vs. 0.600, $P = 0.014$; R^2 : 0.102 vs. 0.076) and CSS in consideration of competing risk for patients (C-index: 0.662 vs. 0.514) with SBA.

3.4. Survival stratified by TLM and TNM stage

On the bias of development and validation for TLM stage, we evaluated patients in different TLM staging. Three-year OS, CSS, and DFS were calculated for all patients and TNM stage I, II, III, and IV. Survival would be calculated in subgroups with ≥ 10 patients. As is shown in the Table 2, when CSS was examined for all patients in the three cohorts, the 3-year survival rate was 72.7–77.2% in patients with TLM I stage, and this decreased to 22.7–17.2% in patients with TLM IV stage. Within the TNM stage III subgroups, one can see a dramatic decrease in 3-year survival end points in patients with TLM stage II (53.2% CSS rate in the development cohort, 61.9% CSS rate in the validation cohort, and 67.7% CSS rate in the test cohort), patients with TLM stage III (33.5% CSS rate in the development cohort, 42.1% CSS rate in the validation cohort, and 45.9% CSS rate in the test cohort), and patients with TLM stage IV (21.6% CSS rate in the development cohort, 32.4% CSS rate in the validation cohort, and 32.4% CSS rate in the test cohort). Besides, it could be also seen from the Table 2 that there were similar 3-year CSS rate between the TNM stage II and Stage III in subgroups of patients with TLM stage II for the development, validation and test cohort. These differences are highlighted in Table 2 and show the importance of the stratification of patients by TLM staging.

In addition, we performed subgroup analysis in the patients with TNM stage II or III SBA. Nearly 75% of patients were included for subgroup analysis in the development (74.4%, 1331/1789), the validation (73.9%, 323/437) and the test cohort (74.1%, 123/166) subgroups. As shown in Supplementary 1, TLM staging could successfully classify TNM stage II or III SBA patients into four subgroups with significant

difference of prognosis (CSS and OS) seen in the development cohort and the validation cohort. As can be seen in Supplementary 1G–J (test cohort), TLM staging could also successfully classify patients based on different risk of recurrence ($P = 0.033$) and CSS ($P = 0.041$) but failed to classify patients into different risk of OS. Comparing prognosis between TNM stage II and TNM stage III SBA with no significant difference in CSS ($P = 0.28$, Supplementary Figure 2C and 2D), OS ($P = 0.93$, Supplementary Figure 2B) and RFS ($P = 0.17$, Supplementary Figure 2C), we found some degree of heterogeneity between the patients, which may explain why the patients could not be classified into the four TLM staging. Next, we tried to classify the patients into TLM stage I/II and TLM stage III/IV. The results showed that the patients with TLM stage III/IV had poorer CSS ($P = 0.005$, Supplementary Figure 2E and 2H), poorer OS ($P = 0.028$, Supplementary Figure 2F) and poorer RFS ($P = 0.012$, Supplementary Figure 2G) compared to the patients with TLM stage I/II.

We then performed subgroup analysis in the patients with low lymph node yield. Using cut-off < 8 to define low lymph node yield, 44.6% (797/1789), 26.1% (114/437) and 58.4% (97/166) of patients in the development cohort, validation and test cohort were included for subgroup analysis, respectively. As shown in the Supplementary Table 2, compared to TNM staging, TLM staging still demonstrated higher accuracy in predicting CSS, OS and RFS in the development cohort, the validation cohort and the test cohort, respectively.

4. Discussion

In the present study, we developed and validated a prognostic staging scheme, TLM staging, for predicting patients with SBA. We incorporated three items, T stage, LODDS classification and M stage into our TLM staging system. We found that this novel TLM staging was more accurate in stratifying SBA patients compared with the 8th TNM staging in the three cohorts.

Unlike the AJCC TNM staging, the current TLM staging consists of LODDS classification instead of N staging. LN status and prognosis of SBA have been previously shown to have positive association [19–21]. Although TNM staging is the main staging system of LN, the

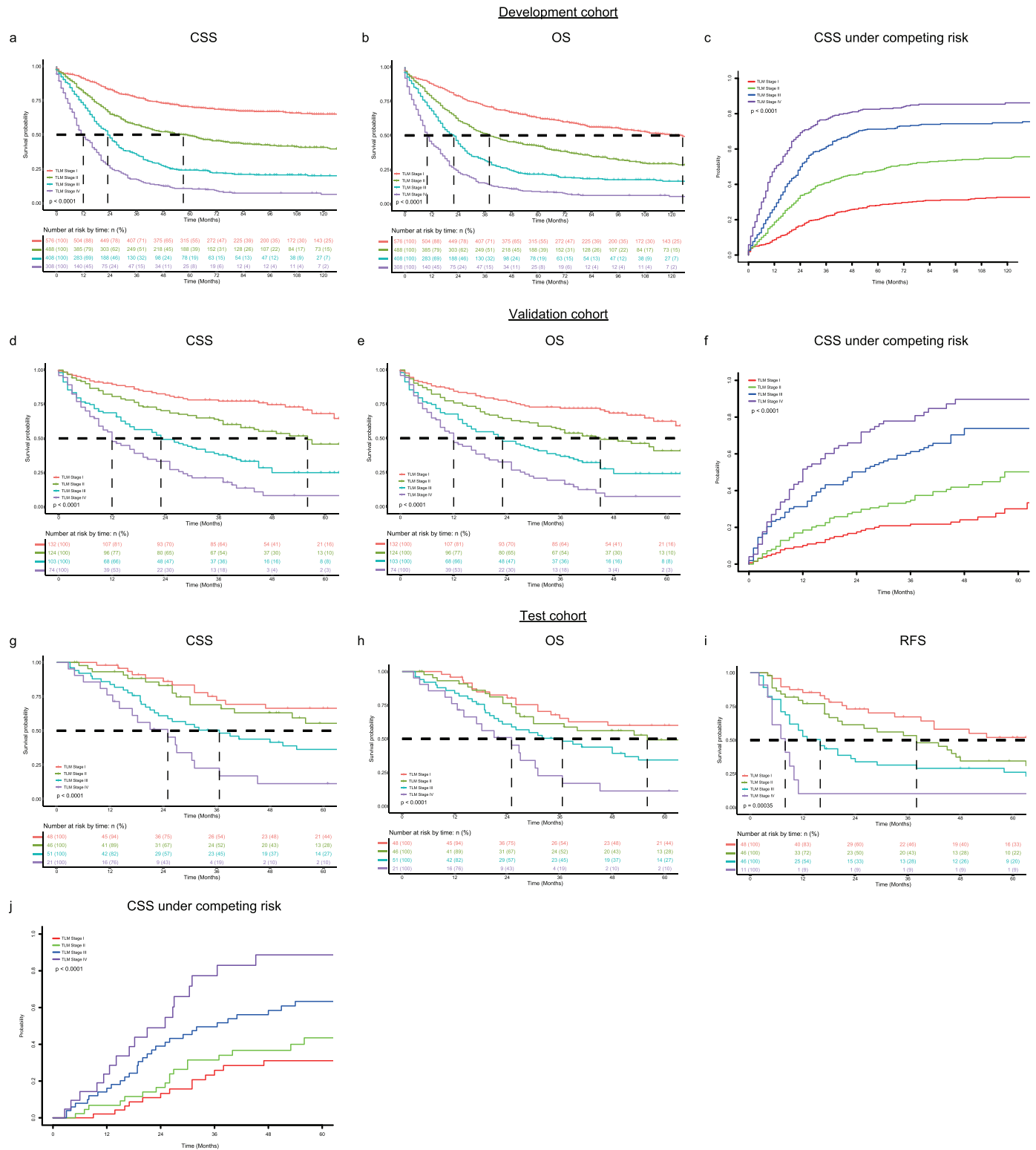


Fig. 2. CSS (A, D, G), OS (B, E, H), RFS (I) and cumulative incidence of SBA-associated death under competing risk model (C, F, J) for the novel TLM staging in the development, validation, and test cohort, respectively. CSS: cancer specific survival; OS: overall survival; RFS: recurrence-free survival; SBA: small bowel adenocarcinoma; TLM: tumor, log odds of positive lymph nodes and metastasis.

prediction accuracy of the N staging for SBAs has been questioned [4,5]. In fact, N staging only records the absolute number of positive LNs without considering the number of retrieved LNs. LODDS, a measure that considers both the number of positive and negative LNs, is more rational than N staging and has demonstrated higher

discriminatory power than the N staging based on our previous study [8]. In addition, we defined specific cut-offs for LODDS of -1.89 and -0.51 for our LODDS classification and validated predictive efficacy of LODDS classification in predicting OS or CSS with higher C-index than LNR or 8th N staging [8].

Table 3

Comparison of novel TLM staging and 8th edition TNM staging in predicting the survival of patients with SBA in different cohorts.

	Development cohort			Validation cohort		Test cohort	
	Harrell's C	Bootstrap	R ²	Harrell's C	R ²	Harrell's C	R ²
CSS							
TLM Stage	0.682	0.682	0.216	0.682	0.195	0.659	0.141
8 th TNM stage	0.650	0.650	0.160	0.654	0.163	0.611	0.102
OS							
TLM Stage	0.662	0.662	0.194	0.654	0.161	0.624	0.108
8 th TNM stage	0.628	0.628	0.130	0.622	0.124	0.580	0.08
CSS under competing risk model							
TLM Stage	0.671	0.671	NA	0.685	NA	0.662	NA
8 th TNM stage	0.637	0.637	NA	0.658	NA	0.614	NA
RFS							
TLM Stage	NA	NA	NA	NA	NA	0.653	0.102
8 th TNM stage	NA	NA	NA	NA	NA	0.600	0.076

TLM: tumor, log odds of positive lymph nodes and metastasis; TNM: tumor, log odds of positive lymph nodes and metastasis; CSS: cancer-specific survival; OS: overall survival; RFS: recurrence-free survival; NA: not available.

In clinical practice setting, SBAs are often diagnosed with local complications such as obstruction or bleeding, which results in emergent surgery for symptom relief but not oncologic resection and LNs examination for N staging [22,23], leading to poor quality of SBAs surgery. Only one resected lymph node from 8.6% (154/1789) patients in the development cohort was sent for histological examination for metastasis. However, it should be noted that the number of lymph nodes examined has been identified as an important risk factor for prognosis [24–27]. Based on some recent studies, the number of lymph nodes retrieved is taken as a surrogate for the quality of surgery [28], with the proposed cutoffs for the optimal number of lymph nodes retrieved ranging from 8 to 17 between studies [24–27]. Previous studies found that duodenal adenocarcinoma had poorer prognosis than jejunal or ileal adenocarcinoma [29], which suggested that duodenal adenocarcinoma and jejunal/ileal adenocarcinoma may be treated in different way. Consistent with this finding, two studies evaluating the number of retrieved lymph nodes separately in duodenal adenocarcinoma [25] and jejunal/ileal adenocarcinoma [24] found 10 as the minimal number lymph nodes retrieved for non-duodenal small bowel adenocarcinoma [24] whereas 15 as the minimal number for duodenal small bowel adenocarcinoma [25], respectively. Now there is need to reach a consensus for the minimal number of retrieved lymph nodes, Based on previous studies [24–27], the latest NCCN clinical practice guidelines recommends the retrieval of at least 8 regional lymph nodes of SBA for evaluation and histological examination of lymph node status [30]. However, in this study, only 49.87% of diagnosed SBAs could reach this standard and could be evaluated for TNM staging with high confidence.

On the other hand, it is well known that for various kind of malignant tumors, the survival outcomes have been improving by periods [31]. However, when we analyzed CSS and OS of patients with SBA stratified by period (Supplementary Figure 2), we found no difference in survival outcomes among different periods, indicating that prognosis of SBAs did not improve with the advancement of technique and periods. The reason behind this finding could be that the percent of SBAs with adequate LN histological examination is low due to emergent need for surgery but not for oncologic resection. As a result, pN staging is underestimated, leading to missed post-operative treatment and poor prognosis.

Considering this situation, our TLM staging may complement TNM staging. In the validation and test cohort, the developed TLM staging had higher C-index than the 8th edition TNM staging in predicting OS, CSS and RFS of patients with SBAs. In addition, as can be seen in Table 2, in subgroups of TLM stage I or II, there was nearly no difference in prognosis of SBA when stratified by the 8th edition TNM staging. While TLM staging prognostically classified SBA patients into

TNM stage II or III SBA, the novel TLM staging could well classify the patients into four different TLM stages with different prognosis. Although TLM staging could not well classify the patients in the test cohort due to some heterogeneity between the patients (Supplementary Figure 2), the patients with TLM stage III/IV still had poorer CSS, OS and RFS compared to patients with TLM stage I/II. Since as high as 44.6%, 26.1% and 58.4% of SBA patients in the development cohort, validation and test cohort, respectively, did not have enough lymph node examination (≥ 8) [30], subgroup analysis was performed in those patients. Results (Supplementary Table 2) showed that TLM staging still had higher predictive efficacy than TNM staging in predicting prognosis in the three cohorts. Therefore, our results suggested that TLM staging may be accurate in predicting survival of patients with SBAs especially SBA patients who do not get enough lymph node examined, after which additional adjuvant therapy could be performed to improve prognosis.

Since the newly developed TLM staging could classify patients with SBA into four groups with different prognosis, groups with poorer survival could be selected for systemic adjuvant treatment. It has been reported that adjuvant chemotherapy could significantly improve TNM stage III SBA patients compared to those receiving only surgical treatment [32]. The combination of a fluoropyrimidine and oxaliplatin appears to be the most effective systemic chemotherapy for disseminated disease [33]. However, the efficacy of adjuvant chemotherapy appear to have minimal impact in improving the prognosis of patients with TNM stage I and II disease [32,33]. Furthermore, there is limited evidence to support the efficacy of radiotherapy and therefore, adjuvant radiotherapy is not recommended for patients with SBA [33]. For SBA patients with metastatic disease, systemic chemotherapy seems to show benefit, whereby the combination of a fluoropyrimidine and oxaliplatin (FOLFOX or CAPOX) appears to be the most effective front-line regimen [33–36]. However, these studies compared the efficacy of adjuvant chemotherapy using TNM staging not TLM staging [33]. Whether our TLM staging could appropriately select patients for adjuvant chemotherapy, especially TLM stage II and stage III patients, needs further investigation.

Our study had few limitations. Firstly, all SBAs in the present study were collected retrospectively, which can be source of inherent bias. The predictive performance of LODDS classification and TLM staging should be assessed in a prospective study. Secondly, information about adjuvant therapy could not be included in the study as no information was available in the SEER database. Further study should be performed to investigate whether adjuvant therapy after surgery contributes to better prognosis stratified by TLM staging. Thirdly, only combinations with at least 10 cases were included for EACCD,

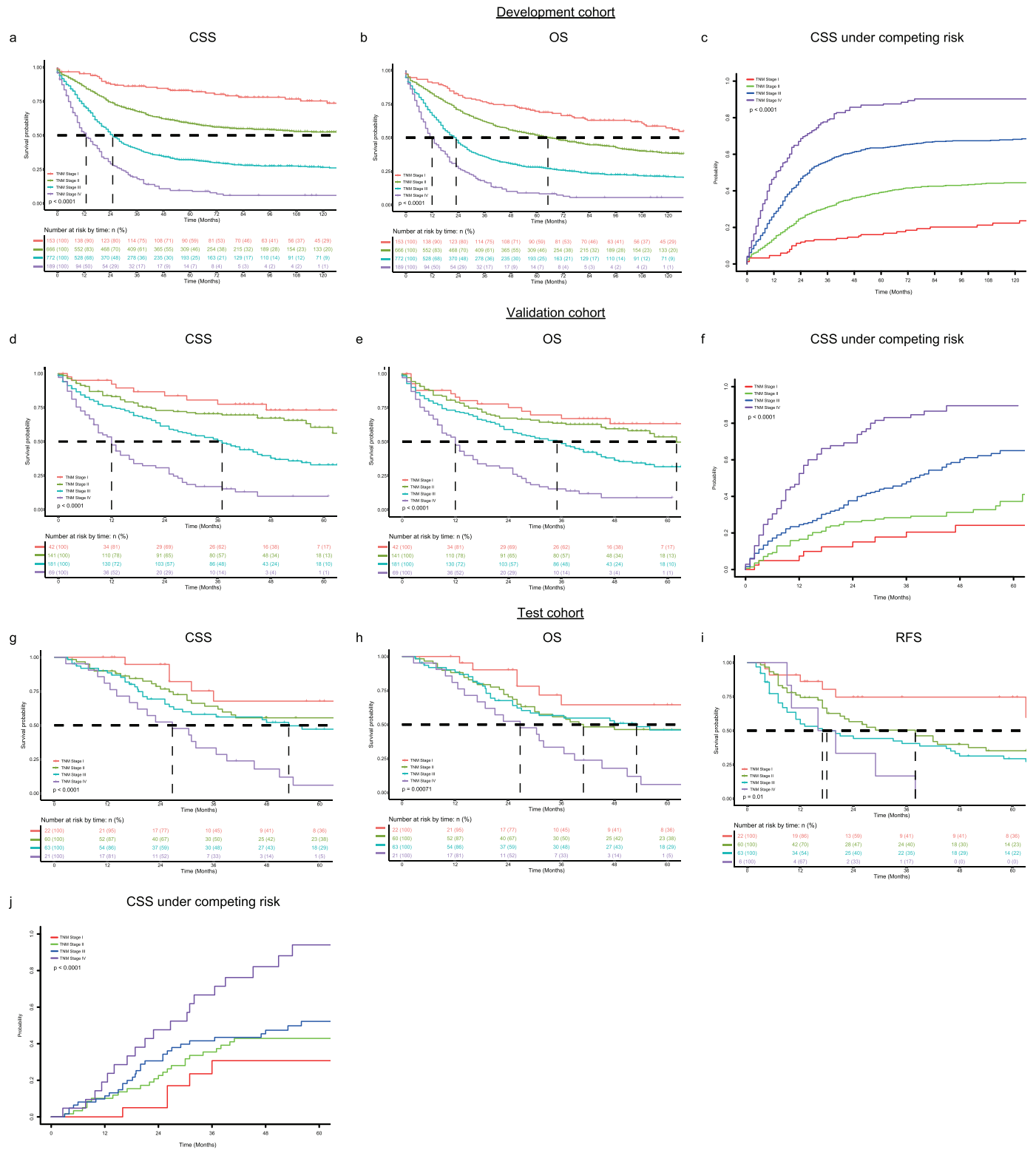


Fig. 3. CSS (A, D, G), OS (B, E, H), RFS (I) and cumulative incidence of SBA-associated death under competing risk model (C, F, J) for the traditional 8th edition TNM staging in the development, validation, and test cohort, respectively. CSS: cancer specific survival; OS: overall survival; RFS: recurrence-free survival; TNM: tumor, log odds of positive lymph nodes and metastasis.

which results in some combinations not classified to corresponding groups. This limitation could be solved as more data become available. Fourthly, use of a large number of patients with SBA diagnosed between 1988 to 2010 to develop the novel TLM staging, may lead to varied survival outcomes among different decades. Since additional analysis comparing survival outcomes among different decades

showed similar survival outcomes (See [Supplementary Figure 2](#)), suggests that bias due to study period is limited. Fifthly, one of the inclusion criteria in the study was patients who had undergone surgery, which led to failure to include patients without a history of surgery, especially those with systematic metastasis. Therefore, TLM stage could not be evaluated for non-operated stage 4 patients. Future

study may be performed to investigate whether preoperative computed tomography imaging could accurately evaluate TLM staging for SBA patients, especially those patients with non-operated stage 4 SBA. Sixthly, patients who had a single lymph node examined were also included in the study, which may affect the reliability of the results in terms of both TNM and TLM staging. However, the percent of patients with a single lymph node examined was lower in the validation cohort (5.3%) and test cohort (6.0%) than in the development cohort (8.6%) and results also showed higher predictive efficacy of TLM staging than that of TNM staging. Future prospective study may focus on inclusion of more patients with enough lymph nodes examined to adjust the novel TLM staging. Lastly, there are some inherent differences between validation/test and discovery cohort (Table 1), results should be interpreted with caution.

In conclusion, we have developed a novel TLM staging, which demonstrated high predictive ability in the prognosis of SBA, and therefore, could serve to complement the TNM staging in patients with SBA.

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Declaration of Interests

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2020.102979.

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