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Establishment of a nomogram model for predicting distant metastasis in pancreatic ductal adenocarcinoma: a comparative analysis of different lymph node staging systems based on the SEER database

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The purpose of this study was to compare the predictive value of different lymph node staging systems and to develop an optimal prognostic nomogram for predicting distant metastasis in pancreatic ductal adenocarcinoma (PDAC). Our study involved 6364 patients selected from the Surveillance, Epidemiology, and End Results (SEER) database and 126 patients from China. Independent risk factors for distant metastasis were screened by univariate and multivariate logistic regression analyses, and a model-based comparison of different lymph node staging systems was conducted. Furthermore, we developed a nomogram for predicting distant metastasis using the optimal performance lymph node staging system. The lymph node ratio (LNR), log odds of positive lymph nodes (LODDS), age, primary site, grade, tumor size, American Joint Committee on Cancer (AJCC) 7th Edition T stage, and radiotherapy recipient status were significant predictors of distant metastasis in PDAC patients. The model with the LODDS was a better fit than the model with the LNR. We developed a nomogram model based on LODDS and six clinical parameters. The area under the curve (AUC) and concordance index (C-index) of 0.753 indicated that this model satisfied the discrimination criteria. Kaplan–Meier curves indicate a significant difference in OS among patients with different metastasis risks. LODDS seems to have a superior ability to predict distant metastasis in PDAC patients compared with the AJCC 8th Edition N stage, PLN and LNR staging systems. Moreover, we developed a nomogram model for predicting distant metastasis. Clinicians can use the model to detect patients at high risk of distant metastasis and to make further clinical decisions.

Keywords Pancreatic ductal adenocarcinoma, Distant metastasis, LODDS, Lymph node staging system, Predictive accuracy, Nomogram model

Abbreviations

SEER	The Surveillance, Epidemiology, and End Results
AJCC	American Joint Committee on Cancer
PLN	Positive lymph node

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LNR	Lymph node ratio
LODDS	Log odds of positive lymph nodes
C-index	Concordance index
AIC	Akaike information criterion
BIC	Bayesian information criterion
ROC	Receiver operating characteristic
AUC	Area under curve
DCA	Decision curve analysis
ELN	Examined lymph node
NB	Net benefit
OR	Odds ratio
CI	Confidence interval

Pancreatic ductal adenocarcinoma (PDAC) is the most common pathological type of pancreatic malignancy and is characterized by an aggressive nature and poor prognosis, with a 5-year survival rate of less than 12%[1–3]. Since 90% of cancer-related deaths are due to metastasis rather than the primary tumor, our focus is primarily on the distant metastasis of cancer[4]. Common sites of distant metastasis in PDAC include the peritoneum and liver, followed by the lungs, bones, and other organs[5]. When patients with PDAC develop distant metastasis, the 5-year survival rate is only 2%[6]. In the past decade, targeted therapies have brought great hope to patients with advanced PDAC. Novel drugs targeting the KRAS gene, such as sotorasib and adagrasib, have shown efficacy and good tolerability in solid tumors, including PDAC, in clinical trials[1,7–10]. Therefore, the timely and effective identification of PDAC patients at high risk of distant metastasis is crucial for their treatment and prognosis. According to the 2023 version of the National Comprehensive Cancer Network (NCCN) guidelines for pancreatic cancer, imaging studies should be performed for PDAC patients suspected of having distant metastasis, including chest, abdominal, and pelvic CT; liver MRI; and PET/CT[11]. However, the sensitivity of imaging studies for detecting metastatic lesions is limited; even the combination of PET/CT and standard CT does not exceed 90% sensitivity. Moreover, repeated use of these imaging methods can increase the psychological and economic burden on patients[11]. Therefore, establishing a simple and practical clinical model for predicting distant metastasis in PDAC patients has significant clinical and economic value.

It is well known that locoregional lymph node metastasis is a significant factor affecting distant metastasis in PDAC patients. The American Joint Committee on Cancer (AJCC) tumor staging system is the most commonly utilized staging system for PDAC. Several researchers have developed a model for predicting distant metastasis of pancreatic malignancies based on the American Joint Committee on Cancer (AJCC) 7th Edition N staging system[12]. In comparison to the 7th version, which defines N classifications as N0 [no positive lymph node (PLN)] and N1 (at least one PLN), the 8th version has revised the N stage to include N0, N1 (1–3 PLN), and N2 (4 or more PLNs). Li et al.[13] discovered that the AJCC 8th Edition N stage was the optimal tool for the lymph node staging system in the investigation of pancreatic neuroendocrine tumors. In addition, lymph node staging systems such as PLN, lymph node ratio (LNR), and log odds of positive lymph nodes (LODDS) have also been proven to have certain predictive value. Tarantino et al.[14] reported that the number of PLNs is a prognostic factor in patients with PDAC. Riediger et al.[15] found that LNR and LODDS are superior to other lymph node staging systems in predicting the prognosis of patients with PDAC. Currently, the predictive value of various lymph node staging systems remains controversial, and studies comparing these systems are lacking. Additionally, the prediction of distant metastasis in PDAC patients is very rare[12]. Therefore, it is very important to conduct a multicenter study with a large sample size and gather follow-up data to compare the predictive abilities of these staging systems and select the optimal system for predicting distant metastasis in patients with PDAC.

Based on the background above, we analyzed data from the Surveillance, Epidemiology, and End Results (SEER) database to compare the ability of different lymph node staging systems to predict distant metastasis in PDAC patients. In addition, we established a new model to predict distant metastasis in PDAC patients and further validated its performance in a Chinese population. This approach will help clinicians develop appropriate treatment plans for patients with PDAC and provide early intervention to improve patient prognosis.

Methods

Patients and data collection

In our study, we searched and obtained clinical data from the SEER database (version 8.4.0.1). The inclusion criteria were as follows: (1) patients were diagnosed histologically with PDAC between 2010 and 2017; (2) patients were diagnosed after the age of 18 years, underwent surgery and had at least 1 examined lymph node (ELN); and (3) the information on clinical and demographic features needed for the study was intact and accessible. In addition, patients diagnosed with autopsies or death certificates were excluded from the study. Figure 1 shows the flow chart for the selection of the study population. Finally, 6364 patients were included in the cohort to study the risk factors for distant metastasis in patients with PDAC and to establish a predictive nomogram. In addition, we retrospectively collected the data of 126 patients with PDAC at The Second Hospital of Dalian Medical University between 2015 and 2020 as an external validation cohort for our study. The inclusion and exclusion criteria for the external validation cohort were consistent with those for the internal cohort.

Data on the following baseline characteristics of patients with PDAC were obtained: age, sex, race, primary site, grade, AJCC 7th Edition T stage, tumor size, ELN, PLN, and recipient status of radiotherapy and chemotherapy. Moreover, the AJCC 8th Edition N stage, LNR and LODDS were added to this basis. The AJCC 8th Edition N stage was derived from the best available data. LNR and LODDS were calculated as follows: $LNR = PLN/ELN$; $LODDS = \log[(PLN + 0.5)/(ELN - PLN + 0.5)]$.

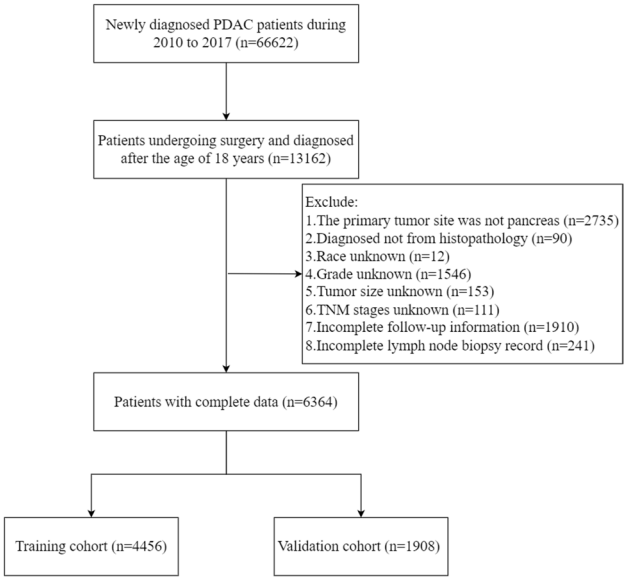

Figure 1. Flowchart of patient selection from the SEER database.

Optimal cutoff points of the variables

The cutoff value for tumor size was determined by the receiver operating characteristic (ROC) curve. The best cutoff point for tumor size was 32 mm, and tumor size was classified into two groups.

Statistical analysis

All analyses were performed using R statistical software (version 4.2.2). The patients were randomly allocated to a training set (n = 4456) or an internal validation set (n = 1908) at a ratio of 7:3. Continuous variables are presented as the mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables are presented as numbers and percentages. Student's t test or the Mann−Whitney U test was used to compare continuous variables, and comparisons between categorical variables were assessed using the chi-square test or Fisher's exact test. Potential risk factors for distant metastasis in PDAC patients were screened using univariate logistic regression analysis. The different lymph node staging systems were respectively included in the multivariate logistic regression analysis to further screen for independent risk factors and establish a corresponding prediction model. We compared the predictive performance of the models based on different lymph node staging systems using the concordance index (C-index), Akaike information criterion (AIC) and Bayesian information criterion (BIC). In addition, we constructed a nomogram based on the filtered models with the highest accuracy in predicting the risk of distant metastasis in patients with PDAC. The accuracy of the established nomogram was evaluated using the C-index and receiver operating characteristic (ROC) analysis, and the discrimination of the nomogram was confirmed using calibration plots. The bootstrap method (1000 bootstrap resamples) was used to conduct internal verification of the nomogram model. Decision curve analysis (DCA) was used to evaluate the clinical utility of the established predictive model. Finally, we analyzed the survival differences between the high-risk and low-risk groups based on the stratification results provided by the nomogram. In the survival analysis, the primary endpoints was OS. Survival curves were plotted using the Kaplan–Meier method, and differences were compared using the log-rank test. Statistical significance was defined as a 2-sided $P < 0.05$.

Ethics approval and consent to participate

The SEER database is public, does not contain any personally identifiable information, and therefore does not require ethical approval. Our request for access to SEER Data has been approved from the National Cancer Institute, USA (reference number 11847-Nov2021). The studies involving human participants underwent a thorough review and received approval from the ethics committee of The Second Hospital of Dalian Medical University.

Results

Patient characteristics

A total of 6364 patients were included in our cohort, 285 (4.5%) of whom developed distant metastasis. Moreover, 4456 patients (70%) were allocated to the training cohort, and the remaining 1908 patients (30%) were assigned to the internal validation cohort. The baseline characteristics of all patients in the current study are summarized in Table 1. In the entire cohort, the median ELN was 17 (interquartile range: 11–23), N1 was 2583 (40.6%) in the AJCC 8th Edition N stage, the median PLN count was 2 (interquartile range: 0 to 4), the median LNR was 0.1 (interquartile range: 0–0.25), and the median LODDS was − 1.95 (interquartile range: − 2.94 to − 1.05). The mean age was 66 years, more patients were male (50.5%), the primary site for the majority of tumors was the head of the pancreas (73.9%), more than half of the patients had tumors smaller than 32 mm (52.6%), 73.8% of patients received chemotherapy, and 30.2% of patients received radiation therapy. There were no differences in

Characteristic	Total (n = 6364)		Training cohort (n = 4456)		Validation cohort (n = 1908)		*P*
Age (mean ± SD)	**66.0 ± 10.3**		**66.0 ± 10.3**		**65.7 ± 10.1**		**0.195**
Sex (n, %)							1
Male	3213	50.5	2250	50.5	963	50.5	
Female	3151	49.5	2206	49.5	945	49.5	
Race (n, %)							0.831
White	5063	79.6	3553	79.7	1510	79.1	
Black	730	11.5	509	11.4	221	11.6	
Other	571	9.0	394	8.8	177	9.3	
Primary site (n, %)							0.737
Head	4705	73.9	3282	73.7	1423	74.6	
Body/tail	1153	18.1	817	18.3	336	17.6	
Other	506	8.0	357	8	149	7.8	
Grade (n, %)							0.667
Well differentiated	632	9.9	437	9.8	195	10.2	
Moderately differentiated	3394	53.3	2367	53.1	1027	53.8	
Poorly and undifferentiated	2338	36.7	1652	37.1	686	36.0	
7th AJCC T stage (n, %)							0.297
T1	302	4.8	199	4.5	103	5.4	
T2	582	9.2	403	9	179	9.4	
T3	5194	81.6	3646	81.8	1548	81.1	
T4	286	4.5	208	4.7	78	4.1	
8th AJCC N stage (n, %)							0.519
N0	2012	31.6	1419	31.8	593	31.1	
N1	2583	40.6	1817	40.8	766	40.1	
N2	1769	27.8	1220	27.4	549	28.8	
Tumor size (n, %)							0.610
≤ 32 mm	3346	52.6	2333	52.4	1013	53.1	
> 32 mm	3018	47.4	2123	47.6	895	46.9	
Radiotherapy (n, %)							0.100
No	4439	69.8	3080	69.1	1359	71.2	
Yes	1925	30.2	1376	30.9	549	28.8	
Chemotherapy (n, %)							0.769
No/Unknown	1667	26.2	1162	26.1	505	26.5	
Yes	4697	73.8	3294	73.9	1403	73.5	
ELN							0.785
Median	17		17		17		
IQR	11,23		11,23		11,24		
PLN							0.183
Median	2		2		2		
IQR	0,4		0,4		0,4		
LNR							0.077
Median	0.1		0.09		0.1		
IQR	0,0.25		0,0.24		0,0.25		
LODDS							0.118
Median	-1.95		-1.95		-1.89		
IQR	-2.94,-1.05		-2.94,-1.10		-2.94,-1.00		
Distant metastasis (n, %)							1
No	6079	95.5	4256	95.5	1823	95.5	
Yes	285	4.5	200	4.5	85	45.5	

Table 1. Demographic and clinicopathological characteristics in PDAC.

clinical characteristics, such as age, sex, race, primary site, grade, tumor size, AJCC 7th Edition T stage, AJCC 8th Edition N stage, radiotherapy and chemotherapy recipient status, PLN, LNR, LODDS or distant metastasis, between the two groups ($P > 0.05$).

Independent risk factors for distant metastasis in patients with PDAC

As shown in Table 2, we conducted univariate logistic analysis of the thirteen potential prognostic factors, and the results revealed eight distant metastasis-related variables in patients with PDAC, namely, age, primary site, grade, tumor size, AJCC 7th Edition T stage, radiotherapy recipient status, LNR and LODDS. Variables with statistical significance in the univariate logistic analysis were included in the multivariate logistic analysis. Considering the potential collinearity between LNR and LODDS, we incorporated these two staging systems separately into the multivariate logistic regression analysis. In our multivariate analysis, LNR and LODDS were found to be independent risk factors for distant metastasis in patients with PDAC (Table 3). In addition, in the two multivariate regression analyses, age, primary site, grade, tumor size, AJCC 7th Edition T stage and radiotherapy recipient status were also confirmed as independent risk factors.

Characteristics	Univariate analysis	
	OR (95% CI)	*P*
Age	0.980(0.967–0.993)	0.003
Sex		
Male	Reference	
Female	1.042(0.785–1.385)	0.774
Race		
White	Reference	
Black	0.851(0.514–1.333)	0.503
Other	0.938(0.543–1.518)	0.805
Primary site		
Head	Reference	
Body/tail	2.942(2.163–3.983)	< 0.001
Other	1.366(0.770–2.268)	0.225
Grade		
Well differentiated	Reference	
Moderately differentiated:	2.390(1.231–5.373)	0.019
Poorly and undifferentiated	3.126(1.603–7.047)	0.002
7th AJCC T stage		
T1	Reference	
T2	1.625(0.567–5.828)	0.401
T3	2.281(0.953–7.467)	0.107
T4	5.156(1.920–18.082)	0.003
8th AJCC N stage		
N0	Reference	
N1	1.210(0.855–1.725)	0.286
N2	1.376(0.950–2.001)	0.092
Tumor size		
≤ 32 mm	Reference	
> 32 mm	2.314(1.720–3.143)	< 0.001
Radiotherapy		
No	Reference	
Yes	0.238(0.145–0.369)	< 0.001
Chemotherapy		
No/Unknown	Reference	
Yes	0.776(0.573–1.061)	0.106
PLN	1.035(0.997–1.072)	0.058
LNR	2.649(1.353–5.002)	0.003
LODDS	1.220(1.096–1.358)	< 0.001

Table 2. Univariate logistic regression of risk factor of distant metastasis in PDAC patients. OR, odds ratio; CI, confidence interval; PLN, positive lymph node; LNR, lymph node ratio; LODDS, the log odds of positive lymph nodes.

Characteristic	LNR		LODDS	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	0.971(0.958–0.985)	< 0.001	0.971(0.958–0.985)	< 0.001
Primary site				
Head	Reference		Reference	
Body/tail	2.846(2.052–3.933)	< 0.001	2.940(2.117–4.069)	< 0.001
Other	1.211(0.674–2.044)	0.495	1.237(0.688–2.088)	0.450
Grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.771(0.950–3.684)	0.095	1.778(0.954–3.698)	0.092
Poorly and undifferentiated	2.329(1.242–4.865)	0.014	2.332(1.244–4.869)	0.014
Tumor size				
≤ 32 mm	Reference		Reference	
> 32 mm	1.749(1.273–2.425)	0.001	1.710(1.244–2.372)	0.001
7th AJCC T stage				
T1	Reference		Reference	
T2	1.107(0.373–4.066)	0.864	1.074(0.361–3.949)	0.904
T3	1.766(0.701–5.948)	0.285	1.658(0.657–5.592)	0.342
T4	3.791(1.312–13.804)	0.023	3.592(1.241–13.091)	0.029
Radiotherapy				
No	Reference		Reference	
Yes	0.207(0.125–0.325)	< 0.001	0.207(0.125–0.324)	< 0.001
LNR	2.243(1.112–4.368)	0.020		
LODDS			1.206(1.078–1.347)	0.001

TABLE 3. Multivariate logistic regression of risk factor of distant metastasis in PDAC patients. OR, odds ratio; CI, confidence interval; PLN, positive lymph node; LNR, lymph node ratio; LODDS, the log odds of positive lymph nodes.

Comparison of LNR and LODDS

A comparison of the two multivariate logistic regression models with a single lymph node staging system in the training cohort is shown in Table 4. The C-indices for LNR and LODDS were 0.747 and 0.753, respectively. The AIC values for LNR and LODDS were 1492.862 and 1487.158, respectively, and the BIC values were 1569.686 and 1563.982, respectively. In predicting distant metastasis in patients with PDAC, the model including LODDS had a higher C-index than did the LNR model. Moreover, both the AIC and BIC values for LODDS were lower than those for the LNR model. These results indicate that the model incorporating LODDS has superior predictive performance compared to the model with LNR. While LNR demonstrated a higher OR and is simpler to calculate, the overall predictive ability of LODDS was found to be stronger.

Diagnostic nomogram model establishment and validation

Based on the independent predictors obtained via optimal multivariate logistic regression, we constructed a risk prediction nomogram model for patients with distant metastasis from PDAC (Fig. 2). ROC analysis of the nomogram revealed that the AUC reached 0.753 in the training cohort and 0.757 in the validation cohort (Fig. 3A,D). The calibration curve in the training and validation cohorts demonstrated good consistency between the predicted results and the actual distant metastasis in PDAC patients (Fig. 3B,E). As seen in the DCA of the two cohorts for the distant metastasis nomogram, the net benefit (NB) of the decision curve of the model was greater than that of the two invalid lines within the range of threshold probabilities between 1–20% and 1–30% (Fig. 3C,F). As a further validation step, we created a Chinese validation cohort and plotted its validation curve. The AUC of the nomogram was 0.677, indicating excellent discriminant ability when applied to Chinese populations (Fig. 3G). The calibration curve demonstrated the best consistency between the nomogram predictions and the actual observations (Fig. 3H). In the external validation cohort, DCA also demonstrated that the nomogram model performed well in clinical practice (Fig. 3I).

System	AIC	BIC	C-index
LNR	1492.862	1569.686	0.747
LODDS	1487.158	1563.982	0.753

Table 4. The comparison of LNR and LODDS. AIC, akaike information criterion; BIC, bayesian information criterion; LNR, lymph node ratio; LODDS, the log odds of positive lymph nodes.

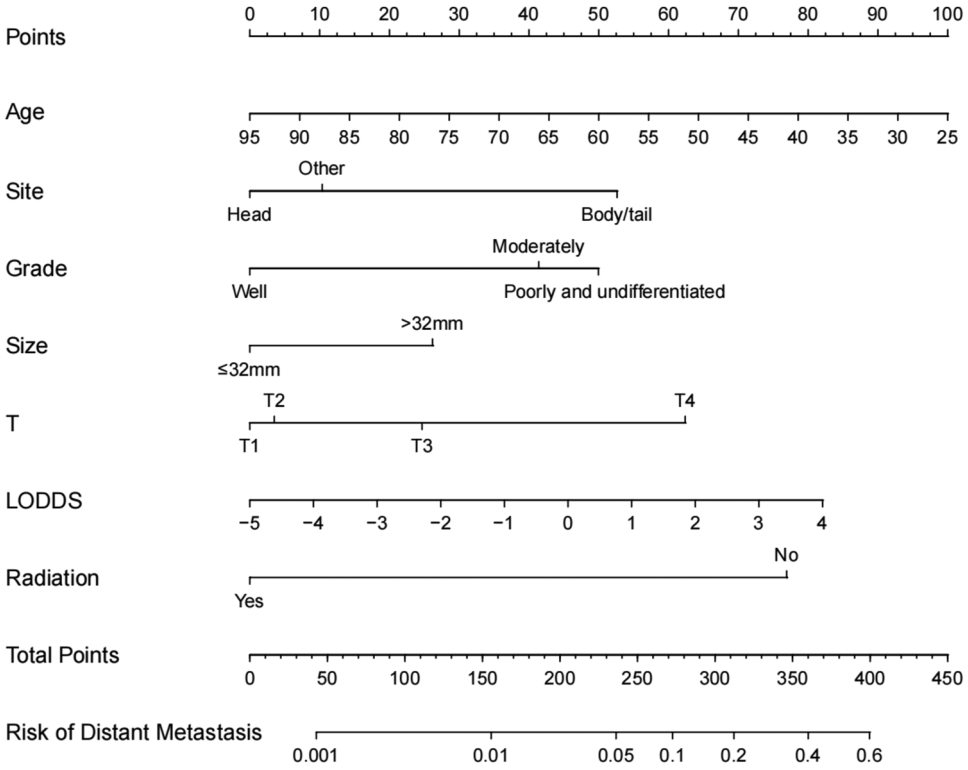

Figure 2. Nomogram for distant metastasis in PDAC patients.

Survival analysis

To further verify the performance of the nomograms, we divided patients into high-risk and low-risk groups based on the total points calculated by the nomograms for distant metastasis risk. The cutoff value of the total points was 229.2. Kaplan–Meier curves showed significant distinctions in OS outcomes stratified by different classifiers in three cohorts (Fig. 4).

Discussion

PDAC is the most prevalent malignancy of the digestive system, except for colorectal and hepatobiliary malignancies, and its incidence is progressively increasing at a rate of 1.03% annually[3,16]. Despite recent notable advances in PDAC treatments, such as chemotherapy, radiotherapy, and immunotherapy, the overall prognosis of patients with PDAC has remained disappointingly unchanged[17]. The majority of patients ultimately succumb to peritoneal or distant metastases. This grim outcome persists even after comprehensive surgical interventions, with distant metastasis and recurrence often being unfortunate yet unavoidable realities[18,19].

Numerous studies have confirmed that radiotherapy, chemotherapy, immunotherapy and targeted therapies can reduce the incidence of distant metastases and increase patient survival rates[6,20,21]. Despite these advancements, the use of imaging technologies, such as CT, MRI, and PET/CT, for screening for distant metastasis is limited by their high costs, leading to reduced proactive monitoring. Furthermore, these techniques are prone to false negatives, potentially delaying the early detection of distant metastases and, consequently, the timely initiation of treatment, resulting in poor patient outcomes. Therefore, accurately predicting the risk of distant metastasis in PDAC patients and developing personalized treatment plans are highly important. Evaluating independent risk factors for distant metastasis in PDAC patients and establishing clinical predictive models hold significant clinical value.

Lymph node metastasis status is an important factor for assessing the possibility of distant metastasis in patients. Therefore, when establishing a prediction model, selecting a more appropriate and accurate lymph node staging system is essential for improving the accuracy of the model. According to the AJCC 7th Edition N system for PDAC, the N stage was divided into two groups based on the presence or absence of regional lymph node metastasis. It is evident that this staging system does not possess sufficient predictive ability for the occurrence of distant metastasis. Compared to solely considering the presence or absence of PLN involvement, a detailed assessment of the number of PLNs in the region provides a better depiction of the extent of regional lymph node metastasis, thus enabling a more accurate prediction of distant metastasis. In the AJCC 8th Edition N stage for PDAC, individuals with 1–3 PLNs were categorized as N1, while those with more than 4 PLNs were categorized as N2. This reclassification further emphasized the importance of the number of PLNs according to the stage of PDAC. Therefore, in our study, we utilized the AJCC 8th Edition N staging rather than the 7th Edition. Unfortunately, our research revealed that the AJCC 8th Edition N stage, including the PLN stage, was not

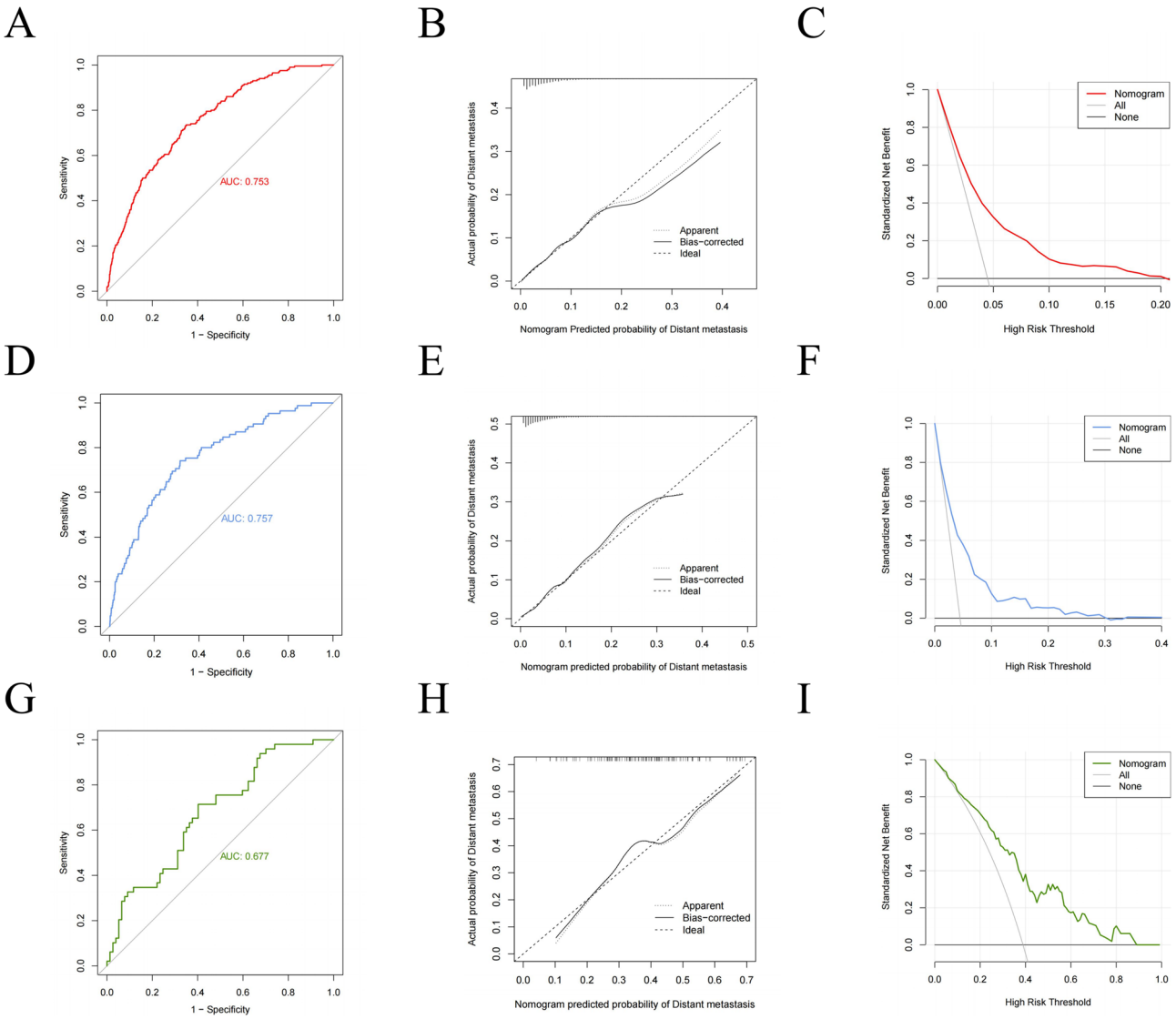

Figure 3. Predictive performance of a nomogram model for predicting distant metastasis in PDAC patients. (**A**) ROC curve analysis to predict distant metastasis in PDAC patients. (**B**) Calibration curve of the nomogram for predicting distant metastasis in PDAC patients. (**C**) Decision curve analysis for distant metastasis in PDAC patients. (**D**) ROC curve analysis of the validation cohort. (**E**) Calibration curve of the nomogram in the validation cohort. (**F**) Decision curve analysis in the validation cohort. (**G**) ROC curve analysis of the external validation cohort. (**H**) Calibration curve of the nomogram in the validation cohort. (**I**) Decision curve analysis in the external validation cohort.

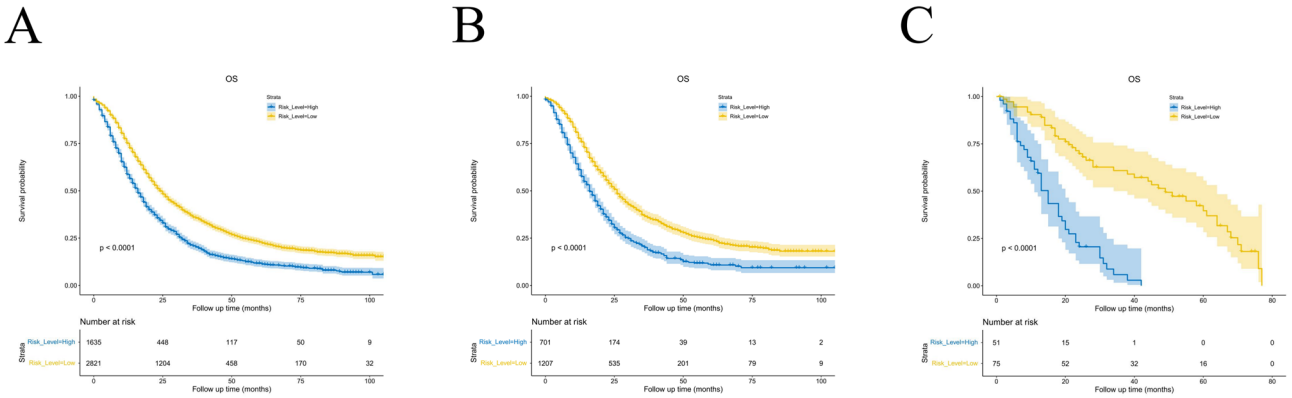

Figure 4. Kaplan–Meier curves of OS for PDAC patients with distant metastasis in low-risk and high-risk groups. (**A**) the training cohort; (**B**) the validation cohort; (**C**) the external validation cohort.

an independent risk factor for distant metastasis in PDAC patients. This finding indicates that a staging system that relies solely on a single lymph node metric, such as the PLN, is insufficient for providing a robust prediction of distant metastasis in PDAC patients. Furthermore, Amin et al.[22] recommended that the minimum number of lymph nodes to be detected is 12, which would enhance the accuracy of the AJCC 8th Edition N stage. However, in real clinical practice, the number of ELNs during surgery cannot be guaranteed due to factors such as patient condition, hospital resources, and surgical technique. Therefore, an effective lymph node staging system should be developed that combines both the ELN and PLN and is easily applicable in clinical settings.

LNR and LODDS staging systems have been increasingly advocated in the academic community due to their incorporation of both the number of PLNs and the number of ELNs, providing improved staging capabilities for metastatic lymph nodes. Wu et al.[23] conducted a retrospective analysis of 177 patients with PDAC who underwent surgical treatment, revealing that the LNR was a significant independent prognostic factor for PDAC. The LNR combines the prognostic impact of both the number of PLNs and the number of ELNs and reduces stage migration to some extent; however, the inherent predictive ability of the LNR is incomplete when the LNR is 0 or 1. In addition, patients with the same LNR but different ELNs were included. By incorporating the number of negative lymph nodes, LODDS provides further predictive information in such situations. Although Riediger et al.[15] found in their study that LODDS does not have a superior advantage over LNR for predicting patient prognosis. Other scholars have confirmed that LODDS can effectively stratify the prognosis of patients with PDAC[24]. This fact was further validated in our study, revealing that its value extends beyond merely predicting patient prognosis.

Considering the lack of consensus in previous studies, we aimed to further summarize the characteristics of different lymph node staging systems based on previous relevant studies. The objective of this study was to compare the ability of four lymph node staging systems to predict distant metastasis in PDAC patients. In our study, we included more than 6000 patients with PDAC who had well-documented lymph node information, and all these patients had clear documentation of distant metastasis status. Through univariate and multivariate regression analyses, we found that in addition to LNR and LODDS, age, primary site, grade, AJCC 7th Edition T stage, tumor size and radiotherapy recipient status factors were also identified as independent risk factors for patients with distant metastasis in PDAC. To obtain the optimal predictive model, we separately combined LNR and LODDS staging systems with the six independent predictive factors mentioned above to construct a comprehensive model. To determine the prognostic value of the LODDS staging system, we calculated the C-index, AIC, and BIC values of the two lymph node staging systems and found that LODDS had the best overall performance.

Furthermore, we found that younger patients with PDAC are more prone to distant metastasis, consistent with the findings of Li et al.[12], particularly for patients younger than 60 years. Similar results have been observed in previous studies focusing on single-organ distant metastasis in PDAC[25,26]. These outcomes suggest that age is a risk factor for distant metastasis in PDAC patients, with younger patients being at greater risk. Therefore, close monitoring of younger patients and conducting prospective studies to understand the underlying mechanisms driving this association are crucial.

Compared to patients with tumors located in the body and tail of the pancreas, patients with tumors in the head of the pancreas are more likely to present symptoms such as jaundice. Therefore, in clinical practice, PDAC in the body and tail of the pancreas is often more challenging to detect early and presents with more severe symptoms than PDAC in the head of the pancreas. When PDAC in the body and tail is identified, the tumor is usually larger in diameter and more prone to distant metastasis than when it is not[27]. Previous studies have shown that PDAC originating from the body and tail of the pancreas is enriched in gene programs involved in tumor cell invasion and epithelial–mesenchymal transition and has a weakened antitumor immune response, increasing tumor aggressiveness[28]. Our predictive model indicated that the risk score for distant metastasis in PDAC of the pancreatic body and tail was significantly greater than that in the head. This finding is consistent with those of previous studies; however, the findings regarding the impact of tumor location on prognosis at different research centers are inconsistent and warrant further investigation[12,29,30].

Tumor differentiation also impacts the occurrence of distant metastasis. In our study, due to the relative scarcity of undifferentiated PDAC samples, we merged undifferentiated samples with poorly differentiated samples to avoid statistical bias. Our analysis revealed that poorer differentiation is associated with a greater risk of distant metastasis, aligning with our existing understanding of tumor biology[31,32]. While previous research has confirmed the value of T staging in predicting PDAC survival, studies focusing on predicting distant metastasis are limited[33,34].

Our study also confirmed that a higher T stage is an independent risk factor for distant metastasis. A previous study utilizing a mathematical model to predict PDAC metastatic capability indicated that the probability of distant tumor metastasis depends on the size of the primary tumor at diagnosis[35]. Our research corroborates these findings, and a multicenter study also confirmed the relationship between tumor size and distant metastasis[36]. However, it is worth noting that small-volume tumors also have significant potential to spread or metastasize to multiple parts or organs of the body[37].

Our analysis revealed that patients who received radiation therapy had a significantly lower risk of distant metastasis than did those who did not. Meng et al.[38] reported that radiation-inducible immunotherapy can be used to prevent distant metastasis of tumors. Based on the results of the present study, radiation therapy appears to play a crucial role in reducing the likelihood of distant metastasis in patients with PDAC. Given these findings, radiation therapy should be considered a necessary treatment option. However, importantly, treatment decisions should be made on a case-by-case basis, accounting for individual patient characteristics, disease stage, and the overall treatment plan.

We developed a nomogram for predicting distant metastasis based on the seven independent predictors mentioned above, including LODDS, age, primary site, grade, AJCC 7th Edition T stage, tumor size and radiotherapy. With this model, the C-index of the nomogram prediction model was 0.753, the C-index of the validation cohort was 0.757, and the C-index of the external validation cohort was 0.677, indicating that the model

had good predictive ability. The calibration curve suggested that the actual probability of distant metastasis corresponded closely with the predicted probability of distant metastasis in patients with PDAC. Additionally, the Kaplan–Meier curves indicate that patients with a low risk of metastasis have significantly better prognoses compared to those with a high risk.

To our knowledge, this is the first study in which LODDS was used as a predictive tool for distant metastasis in PDAC patients. The results demonstrated that LODDS outperformed the AJCC 8th Edition N stage, PLN and LNR. Moreover, we established a rare nomogram that demonstrated excellent predictive performance for distant metastasis in patients with PDAC. The prediction model can assist clinicians in identifying PDAC patients at high risk for distant metastasis. Facilitating close monitoring of these individuals and supporting timely treatment when necessary can ultimately improve the poor prognosis of these patients.

This study has several limitations. The observed rate of distant metastasis in our cohort was 4.5%, which included patients who were Stage IV at presentation and underwent surgery. This scenario, while uncommon, is possible in certain clinical contexts where surgery may be deemed appropriate based on patient condition and preferences[39]. This might have contributed to the lower observed rate of metastasis, as our stringent inclusion criteria focused on patients with complete clinical and follow-up data. Future studies should consider broader inclusion criteria to better capture the incidence of distant metastasis across a more diverse patient population. Second, some vital information related to the tumor, such as the level of albumin, bilirubin, and CA199 and specific regimens for radiation therapy and chemotherapy, was not recorded in the SEER database, possibly affecting the accuracy of the prediction model. Third, all the lymph node-related information was obtained through surgical procedures. Therefore, our model may not be applicable to patients who have not undergone surgery and thus lack lymph node information. Despite these limitations, our study is the first to demonstrate the better predictive value of the LODDS staging system, and we incorporated it into a predictive nomogram for distant metastasis in PDAC patients.

Conclusion

For patients with PDAC, the LODDS staging system seems to have a superior ability to predict distant metastasis compared with the American Joint Committee on Cancer (AJCC) 8th Edition N stage, PLN and LNR. Based on data from the SEER database, we also found that age, primary site, grade, AJCC 7th Edition T stage, tumor size and radiotherapy recipient status were found to be independent risk factors for distant metastasis in patients with PDAC. Moreover, we developed a visual nomogram model that predicts distant metastasis in patients with PDAC. Clinicians can use this model to identify patients at high risk of distant metastasis and take further clinical measures to improve patient prognosis.

Data Availability

The data supporting the findings of this study are accessible from the corresponding author upon a reasonable request.

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Author contributions

WLM designed and constructed the study. LYC and GMW conceived the study and participated in its design and coordination. LYC and SYL were responsible for data collection and collation. LYC analyzed the data and wrote the first draft, which was collated and revised by GMW. All authors read and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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