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A Prognostic Nomogram for Disease-Specific Survival in Patients with Pancreatic Ductal Adenocarcinoma of the Head of the Pancreas Following Pancreaticoduodenectomy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCE Huang-bao Li
ACDF Jun Zhou
ABCE Feng-qing Zhao

Department of Hepatobiliary and Pancreatic Surgery, First Hospital of Jiaxing, First Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang, P.R. China

Corresponding Author: Feng-qing Zhao, e-mail: drfengqingzhao@163.com
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Background: This study developed and validated a nomogram to predict patient prognosis for pancreatic ductal adenocarcinoma (PDAC) of the head of the pancreas following pancreaticoduodenectomy.

Material/Methods: Retrospective data were obtained from 4,383 patients with PDAC of the head of the pancreas who underwent pancreaticoduodenectomy between 2004–2013 from 11 Registries Research Data of the Surveillance, Epidemiology,and End Results (SEER) database. Cox proportional hazards model was used to identify independent risk factors. The predictive accuracy of the nomogram was determined by the concordance index (C-index) and calibration curve. The results were externally validated by comparison with data from 1,743 patients from 7 other Registries Research Data.

Results: Of the 4,383 patients in the training dataset, median disease-specific survival (DSS) was 17.0 months (range, 1.0–131 months), and postoperative 1-year, 3-year, and 5-year DSS rates were 70.3%, 26.1%, and 16.8%, respectively. Multivariate analysis showed that patient sex, age, tumor grade, regional lymph nodes examined, positive regional lymph nodes, tumor size, extent of local invasion, and tumor metastases were independent risk factors for DSS. The C-index of the internal validation dataset for prediction of DSS was 0.64 (95% CI, 0.63–0.65), which was superior to the American Joint Committee on Cancer (AJCC) staging, 0.57 (95% CI, 0.56–0.58) (P<0.001). The 5-year DSS rates and median DSS time for patients in the low-risk group were significantly greater compared with high-risk group (P<0.001).

Conclusions: A validated prognostic disease-specific nomogram for patient survival in PDAC of the head of the pancreas following pancreaticoduodenectomy was developed.

MeSH Keywords: Carcinoma, Pancreatic Ductal • Nomograms • Pancreaticoduodenectomy

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Background

In 2017, in the United States, the prevalence of pancreatic cancer was 9% of all malignancies, and pancreatic cancer was the ninth most common type of cancer, but was the fourth most common cause of mortality from cancer, with 53,670 estimated new patients and 43,090 estimated deaths from pancreatic cancer [1]. For PDAC of the head of the pancreas, surgical resection by pancreaticoduodenectomy (Whipple procedure) remains the primary treatment option. However, because the rate of detection of early-stage PDAC remains low and this malignancy progresses rapidly, these factors account for the poor prognosis for patients with PDAC.

According to the data on 31,523 patients with PDAC of the head of the pancreas available in the Surveillance, Epidemiology, and End Results (SEER) database from 2004–2014, only 25.6% of patients (8,075/31,523) underwent pancreaticoduodenectomy. Even for patients treated with surgery, the median survival time was less than two years. Although the prognosis of PDAC of the head of the pancreas is poor, clinicians still need an effective prognostic tool to predict patient survival rates and to plan patient clinical management.

The current staging guidelines from the American Joint Committee on Cancer (AJCC) are widely used in clinical practice to predict the prognosis of pancreatic cancer and to guide radiotherapy and chemotherapy. However, the current AJCC prognostic guidelines that use the tumor, lymph node, and metastasis (TNM) status for PDAC do not include other possible variables that affect patient prognosis following surgery. Therefore, more accurate disease-specific predictive models are still required for patients with PDAC of the head of the pancreas who undergo radical surgery with pancreaticoduodenectomy [2].

The nomogram is a simple multivariate predictive model, which can incorporate several variables that influence disease prognosis [3]. Recently, disease-specific nomograms have been increasingly used to predict prognosis for patients with a variety of malignant tumors [2,4–8]. However, there have been few studies on the use of nomograms in pancreatic ductal adenocarcinoma, and the models that have been developed have shown limited predictive ability [9–12]. To our knowledge, at present, no previous studies have been undertaken to develop a nomogram to predict patient prognosis for PDAC of the head of the pancreas following pancreaticoduodenectomy.

Therefore, the purpose of the present study was to develop and validate a nomogram that could be used for individualized survival assessment in patients with PDAC of the head of the pancreas following treatment with pancreaticoduodenectomy, to guide follow-up clinical treatment.

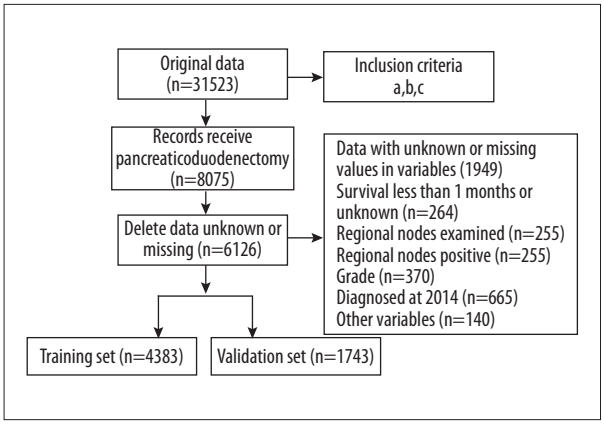

Figure 1. Flowchart of the case selection criteria for patients with pancreatic ductal adenocarcinoma of the head of the pancreas who underwent pancreaticoduodenectomy.

Material and Methods

Patient datasets and study design

The training (or model) and internal validation dataset included retrospective data from 4,383 patients with pancreatic ductal adenocarcinoma (PDAC) of the head of the pancreas who underwent pancreaticoduodenectomy between 2004–2013. Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program database from the SEER 11 Registries Research Data. The external validation set included clinicopathologic data from 1,743 patients, extracted from the other 7 Registries Research Data, from Connecticut, Hawaii, Iowa, New Jersey, New Mexico, Rural Georgia, and San Jose-Monterey. The inclusion and exclusion criteria for external validation set were the same as for the training dataset. Figure 1 is a flowchart of the study design, including the inclusion and exclusion criteria for case selection.

All patients were diagnosed with PDAC of the head of the pancreas by histopathological examination. Demographic and clinicopathologic variables were documented for all patients studied. The variables included sex, age at diagnosis, race, marital status at diagnosis, tumor grade, regional lymph nodes examined, positive regional lymph nodes, tumor size, the extent of local invasion, the presence of metastases, the American Joint Committee on Cancer (AJCC) stage, the cause of death, and postoperative survival (in months). The end of follow-up was December 2014, and the primary endpoint was cause-specific death.

In addition to a histologically-confirmed diagnosis of PDAC of the head of the pancreas, the patient inclusion criteria included the following: (a) a confirmed primary site in the head of the pancreas (SEER: CS Schema v0204+: PancreasHead); (b)

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ductal adenocarcinoma (SEER: 8500), adenocarcinoma (SEER: 8140); (c) a primary tumor of the pancreas with no evidence of any other primary site, and no previous history of malignancy; and, patients who underwent pancreaticoduodenectomy (SEER: Surg Prim Site (1998+): 35, 36, 37, 60, 70).

The following were exclusion criteria: an unknown number or no regional lymph nodes examined; unknown metastatic involvement of regional lymph nodes; postoperative survival of <1 month (as this usually occurs due to surgical complications) or an unknown postoperative survival time; missing or unknown data on other key variables. All patients required follow-up for at least one year after pancreaticoduodenectomy. Data from patients who were diagnosed in 2014 were excluded.

Statistical analysis

The Mann-Whitney U test was used for continuous variables with a non-normal distribution of patient data at baseline, and the continuous variables were transformed into categorical variables to match with the nomogram. The best cut-off points of continuous variables were identified by X-tile bioinformatics software for outcome-based optimization [13]. Categorical variables were grouped according to clinical findings. Independent risk factors were screened using a forward stepwise Cox proportional hazard model and SPSS version 22.0. The disease-specific survival (DSS) rate and the median DSS were calculated using a life (actuarial) table method.

The nomogram was developed based on the independent risk factors and by using the package of rms package in the R Project for Statistical Computing version 3.4.0 (*http://www.r-project.org/*). The discrimination of the nomogram was assessed by Harrell's C-index (the concordance statistic or C-statistic), which could estimate the probability between the observed and predicted DSS[14]. A random resampling procedure (bootstrapping) with 1,000 resamples was used for the internal validation, and the nomogram was externally validated with the validation dataset. Comparisons between the DSS derived from the developed nomogram and the AJCC staging system were performed using the rcorrp.cens package in R and were assessed by the C-index. Based on the scores of each variable, the total DSS scores for each patient could be calculated. Then, according to the scores, the patients were divided into a low-risk group, a moderate-risk group, and high-risk group. The 1-year, 3-year, and 5-year survival rates and the median DSS time of each group were calculated, and the Kaplan-Meier survival curves were drawn. P<0.05 was considered as statistically significant.

Results

Patient clinicopathologic characteristics

Table 1 summarizes the clinicopathologic and demographic characteristic of the patients studied. The training and internal validation dataset included retrospective data from 4,383 patients with pancreatic ductal adenocarcinoma (PDAC) of the head of the pancreas who underwent pancreaticoduodenectomy with data obtained from 11 Registries Research Data of the Surveillance, Epidemiology, and End Results (SEER) program database. The external validation set included clinicopathologic data from 1,743 patients, which were extracted from the other seven Registries Research Data.

Disease-specific survival (DSS)and independent risk factors in the training dataset

The median disease-specific survival (DSS) was 17.0 months (range, 1.0–131 months), and the postoperative 1-year, 3-year, and 5-year DSS rates were 70.3%, 26.1%, and 16.8%, respectively. Multivariate analysis showed that sex, age, tumor grade, regional nodes examined, positive regional lymph nodes, tumor size, the extent of local invasion, and the presence of metastases were independent risk factors for DSS (Table 2).There was no statistical significance in DSS between marital status or race.

The prognostic nomogram for DSS

The nomogram that was generated via the Cox proportional hazards model, including all significant independent prognostic factors for DSS in the training dataset, is shown in Figure 2. The C-index of internal validation for the DSS prediction was 0.64 (95% CI, 0.63–0.65), The calibration curves for the probability of postoperative DSS at 3 years or 5 years showed that there was good consistency between the actual observation and the prediction(Figure 3A, 3B). The C-index of the nomogram was superior to the AJCC staging system, which was 0.57 (95% CI, 0.56–0.58) (P<0.001). The score of each variable is shown in Table 3. Patients with a probability score of <160, 160–190, and>190 were assigned to the low-risk group, the moderate-risk group, and the high-risk group, respectively.

Figure 4 shows the Kaplan-Meier DSS curves separated by nomogram-based grouping. The 5-year DSS rates of the low-risk group, the moderate-risk group, and the high-risk group were 26.7%, 12.5%, and 7% respectively; the median DSS time was 27.8 months,19.0 months, and 13.9 months, respectively. The 5-year DSS rates and median DSS time of patients in the low-risk group were significantly increased when compared with those of patients in the high-risk group (P<0.001).

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Table 1. Demographic and clinicopathologic characteristics of the patients with pancreatic ductal adenocarcinoma of the head of the pancreas who underwent pancreaticoduodenectomy.

Demographic or characteristic	Training dataset		Validation dataset		P
	No. of patients	%	No. of patients	%	
Sex					0.789
Male	2227	50.8	879	50.4	
Female	2156	49.2	864	49.6	
Age, years					
Median(range)	65 (29–94)		66 (32–93)		0.013
Race					<0.001
White	3589	81.9	1453	83.4	
Black	496	11.3	117	6.7	
Others	298	6.8	113	9.9	
Marital status					0.552
Yes	2743	62.6	1105	63.4	
No	1640	37.4	638	36.6	
Grade					0.06
Well differentiated	452	10.3	147	8.4	
Moderately differentiated	2255	51.4	884	50.7	
Poorly differentiated	1642	37.5	694	39.8	
Undifferentiated	34	0.8	18	1.0	
Regional nodes examined					
Median (range)	15 (1–73)		14 (1–78)		0.021
Regional nodes positive					
Median (range)	2 (0–27)		2 (0–21)		0.064
Tumor size, mm					
Median(range)	30 (1–370)		30 (1–500)		0.987
Extension range					0.001
Localization	752	17.2	253	14.5	
Peripancreatic	966	22.0	458	26.3	
Bile duct and periampullary	1902	43.4	760	43.6	
Adjacent organ	763	17.4	272	15.6	
Metastasis					0.359
No	4197	95.8	1678	96.3	
Yes	186	4.2	65	3.7	
AJCC stage					0.001
IA	134	3.1	48	2.8	
IB	224	5.1	69	4.0	
IIA	804	18.3	354	20.3	
IIB	2858	65.2	1171	67.2	
III	187	4.3	38	2.2	
IV	176	4.0	63	3.6	

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Table 2. Multivariate analysis of the training dataset.

Variable	HR	95% CI	P
Sex			
Male	1		
Female	0.911	0.849–0.976	0.008
Age, years			<0.001
≤65	1		
66–72	1.127	1.03–1.234	0.010
≥73	1.258	1.159–1.364	<0.001
Grade			<0.001
Well differentiated	1		
Moderately differentiated	1.520	1.334–1.732	<0.001
Poorly differentiated	1.864	1.631–2.13	<0.001
Undifferentiated	2.492	1.724–3.603	<0.001
Regional nodes examined			<0.001
≤9	1		
10–14	0.835	0.758–0.92	<0.001
≥15	0.661	0.605–0.722	<0.001
Regional nodes positive			<0.001
0	1		
1–2	1.406	1.281–1.545	<0.001
3–5	1.739	1.568–1.929	<0.001
≥6	2.173	1.932–2.445	<0.001
Tumor size, mm			<0.001
≤24	1		
25–34	1.204	1.095–1.323	<0.001
≥35	1.377	1.256–1.51	<0.001
Extension range			<0.001
Localization	1		
Peripancreatic	1.295	1.151–1.457	<0.001
Bile duct and periampullary	1.261	1.134–1.402	<0.001
Adjacent organ	1.536	1.356–1.739	<0.001
Metastasis			<0.001
No	1		
Yes	1.663	1.415–1.953	<0.001

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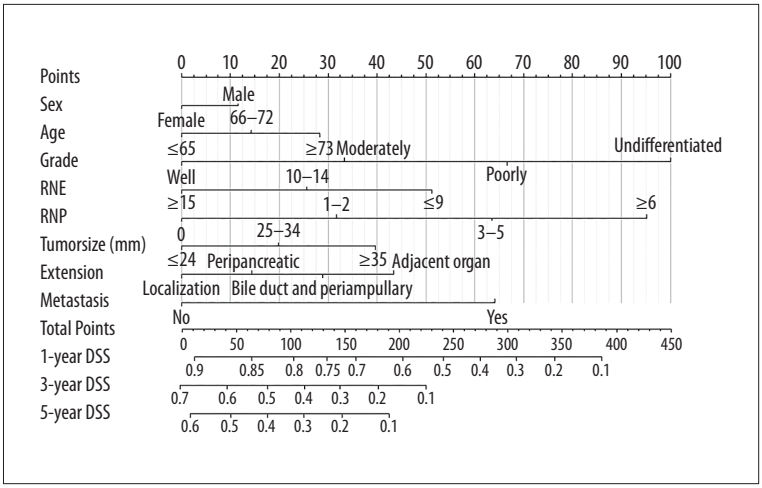

Figure 2. Nomogram for predicting the 1-year, 3-year, and 5-year disease-specific survival(DSS) probabilities in patients with pancreatic ductal adenocarcinoma of the head of the pancreas following pancreaticoduodenectomy. RNE – regional nodes examined; RNP – regional nodes positive; DSS – disease-specific survival.

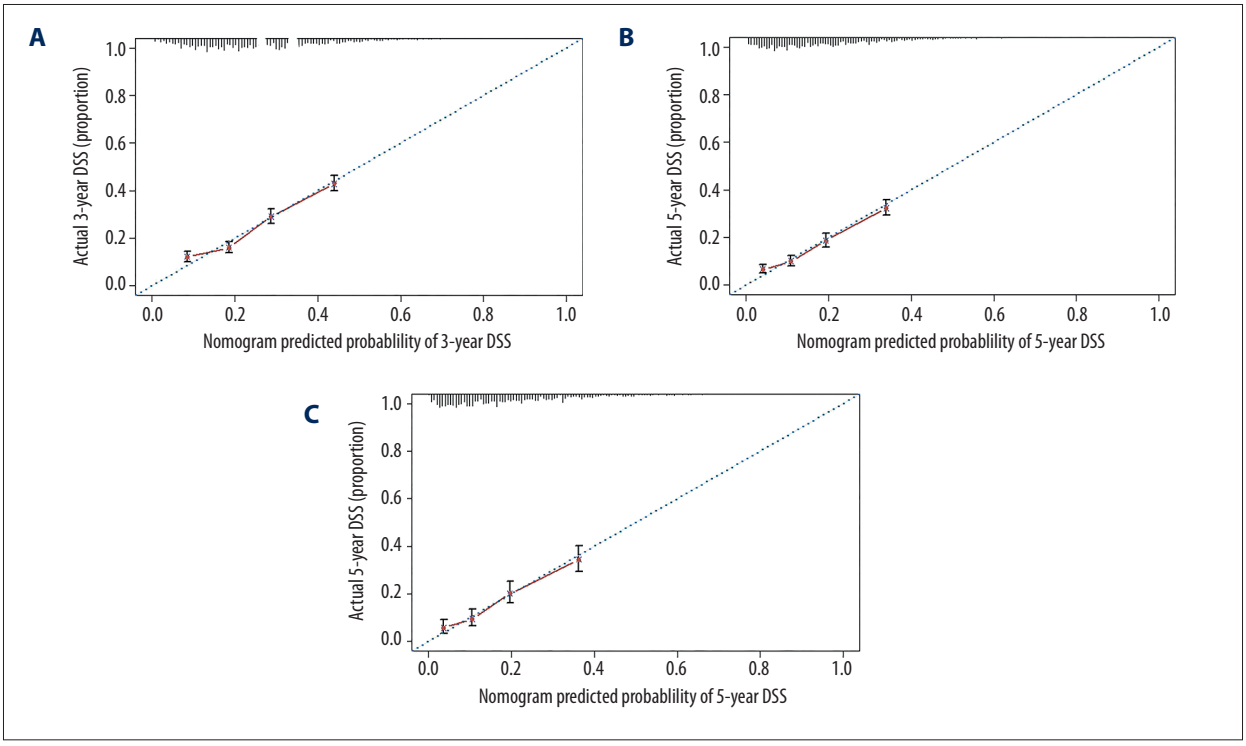

Figure 3. The calibration curves for predicting 3-year and 5-year disease-specific survival (DSS)in patients with pancreatic ductal adenocarcinoma of the head of the pancreas following pancreaticoduodenectomy. (**A**) The calibration curve for predicting patient survival at 3 years, in the training dataset. (**B**) The calibration curve for predicting patient survival at 5 years, in the training dataset. (**C**) The calibration curve for predicting patient survival at 5 years, in the validation dataset. The nomogram-predicted probability of disease-specific survival (DSS) is plotted on the x-axis; the actual DSS is plotted on the y-axis.

Validation of the predictive accuracy of the nomogram for DSS

In the validation dataset, the median DSS time was 18.0 months (range, 1.0–131 months), and the 1-year, 3-year,5-year DSS rates were 74.3%, 28.8%, and 17.3%, respectively. The C-index of the nomogram for DSS prediction was 0.65 (95%CI, 0.63–0.67), and the calibration curve showed that there was good consistency between the actual observation and the prediction in the probability of 5-year survival (Figure 3C).

Discussion

In this study, retrospective data from a total of 6,126 patients with pancreatic ductal adenocarcinoma (PDAC) of the head

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Table 3. The scores of the variables.

Variable	Score	Variable	Score
Sex		Regional nodes positive	
Male	11.5	0	0
Female	0	1–2	31.5
Age, years		3–5	63.5
≤65	0	≥6	95
66–72	14	Tumor size, mm	
≥73	28	≤24	0
Grade		25–34	20
Well differentiated	0	≥35	40
Moderately differentiated	33	Extension range	
Poorly differentiated	66.5	Localization	0
Undifferentiated	100	Peripancreatic	14.5
Regional nodes examined		Bile duct and periampullary6	29
≤9	51	Adjacent organ	43.5
10–14	25.5	Metastasis	
≥15	0	No	0
		Yes	64

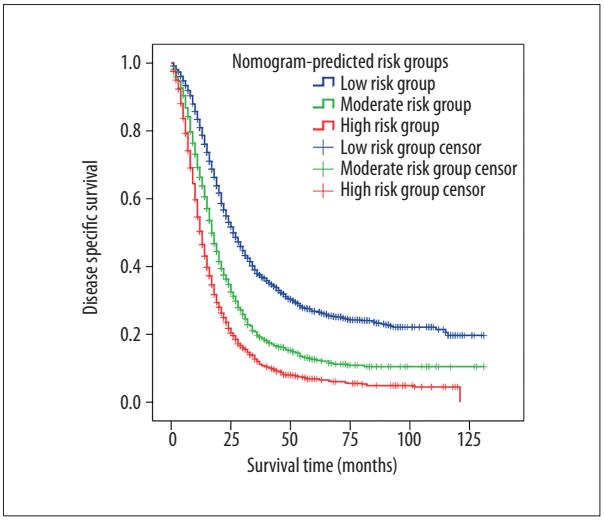

Figure 4. Kaplan-Meier survival curves for patients with pancreatic ductal adenocarcinoma of the head of the pancreas following pancreaticoduodenectomyaccording to thenomogram-based grouping. The P-value (P<0.001) was determined by the log-rank test.

of the pancreas who underwent a pancreaticoduodenectomy (Whipple procedure) between 2004–2013 were reviewed from the Surveillance, Epidemiology, and End Results (SEER) program database. A nomogram was constructed and validated, based on the clinicopathologic findings from the patients in the SEER database. The validated prognostic disease-specific survival (DSS) nomogram for patients with PDAC of the head of the pancreas following pancreaticoduodenectomy was developed and found to be superior to the current American Joint Committee on Cancer (AJCC) staging system for predicting patient survival.

Currently, several prognostic nomograms have been developed for intraduct papillary mucinous tumors of the pancreas [15–17], but the model used in pancreatic adenocarcinoma was infrequently. Are et al. developed a preoperative nomogram based on the presence of comorbidities to predict the risk of postoperative mortality of patients who underwent pancreatectomy, but the defect of this nomogram was by the lack of definition of pancreatic cancer and the fact that it can only predict postoperative mortality [10]. A nomogram established by Panicciaet al. identified that the number of lymph nodes involved, administration of adjuvant chemotherapy, and the AJCC T-stage were the main three variables associated with long-term survival of more than ten years [9]. However, the median survival time of PDAC is less than 17 months, and so the model is not suitable for majority patients with pancreatic cancer [9]. The nomogram developed by Brennan et al. [5] included a large number of variables, such as tumor margins on resection, patient weight loss, and portal vein resection in the study, but the C-index of the model was 0.64, which may be explained by the fact that the study included distal PDAC which has a worse prognosis that PDAC of the head of the pancreas [18]. The nomogram established by Xu et al. [11]

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showed high predictive accuracy for the prognosis of PDAC, but the development of the model was based on data from a single center with a small study population, and the standard values of the variables were inconsistent.

Recently, a multi-institutional validation study of the AJCC (8th Edition) has proposed changes for the T and N stages in patients with PDAC, as the tumor size and positive regional lymph nodes may not be among the most important clinical factors in terms of patient prognosis [19].There might still be many variables that have an impact on the prognosis of PDAC that are not taken into consideration in the AJCC TNM staging system which is used for all malignant tumors, which explains its limited predictive accuracy in terms of patient prognosis.

In the present study, the aim was to develop and validate a nomogram to overcome the limitations of the AJCC TNM system and the previously developed nomograms. The findings of the study showed that when the nomogram was applied to PDAC of the head of the pancreas in patients who had pancreaticoduodenectomy, in addition to the tumor size, positive regional lymph nodes, and lymph node metastasis, other variables, including gender, age, tumor grade, regional nodes examined, and the extent of local invasion were also risk factors for prognosis by multivariate regression analysis. The predictive ability of the nomogram showed a significantly better ability to discriminate patient prognosis when compared with the AJCC stage (C-index, 0.64 *vs.* C-index, 0.57) (P<0.001). Also, in practical terms, the variables used in the nomogram are easily obtained in patients with PDAC of the head of the pancreas after surgery, and the Kaplan-Meier DSS curve verified the grouping effect of nomogram-predicted survival probabilities. The probability score of <160, 160–190, and >190 could be used to assign patients with PDAC of the head of the pancreas following pancreaticoduodenectomy into a low-risk group, a moderate-risk group, and a high-risk group, respectively. Patients in the low-risk group in this model had a better prognosis. Clinicians can immediately and accurately predict the prognosis and provide useful information for postoperative related treatment. Overall, the internal and external validation suggested that there was good consistency between the actual observation and the prediction in the probability of the 3-year and 5-year survival (Figure3).

This study had several limitations. Demographic and clinicopathologic variables were analyzed, but no tumor biomarker analysis was included, for example, CA199, and latent transforming growth factor β binding protein 2 (LTBP2) [20]. The effects of treatment with radiotherapy and chemotherapy were not analyzed, which can affect prognosis [21]. The use of the open access data from the SEER database did not include biomarkers data, radiotherapy and chemotherapy data, major comorbidities, smoking status, or details on immune status. The use of the medical care database containing radiotherapy and chemotherapy also had major limitations as, for example, it only contained information of patients who were more than 65 years-of-age. Therefore, in future, the prognostic disease-specific nomogram developed in this study should undergo external validation using an independent dataset.

Conclusions

In this study, a validated prognostic disease-specific nomogram for patient survival in pancreatic ductal adenocarcinoma (PDAC) of the head of the pancreas following pancreaticoduodenectomy was developed. Clinicopathologic variables, including patient sex, age, tumor grade, number of regional nodes examined, positive regional lymph nodes, tumor size, the extent of local invasion, and the presence of metastases were independent risk factors for postoperative prognosis. Although this was a preliminary study, the findings support that the nomogram was predictive of disease-specific survival (DSS) in patients with PDAC of the head of the pancreas following pancreaticoduodenectomy and that the model should be evaluated in future clinical studies.

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Conflict of interest

None.

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