Original Article

Development and external validation of a prognostic nomogram to predict survival in patients aged ≥60 years with pancreatic ductal adenocarcinoma

Binjiao Zheng[1#], Gangfeng Ding[2#], Guangrong Lu[3], Lili Li[4]^

[1]School of Laboratory Medicine and Life Sciences, Wenzhou Medical University, Wenzhou, China; [2]The First Clinical Medical College of Wenzhou Medical University, Wenzhou, China; [3]Department of Gastroenterology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China; [4]Department of Medical Oncology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Contributions: (I) Conception and design: L Li; (II) Administrative support: G Lu; (III) Provision of study materials or patients: B Zheng; (IV) Collection and assembly of data: G Ding; (V) Data analysis and interpretation: G Lu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Lili Li, MD. Department of Medical Oncology, The First Affiliated Hospital of Wenzhou Medical University, No. 2 Fuxue Lane, Wenzhou 325000, China. Email: 15088943401@126.com or lilili@wzhospital.cn.

Background: Pancreatic ductal adenocarcinoma (PDAC), which accounts for the vast majority of pancreatic cancer (PC), is a highly aggressive malignancy with a dismal prognosis. Age is shown to be an independent factor affecting survival outcomes in patients with PDAC. Our study aimed to identify prognostic factors and construct a nomogram to predict survival in PDAC patients aged ≥60 years.

Methods: Data of PDAC patients aged ≥60 years were collected from the Surveillance, Epidemiology, and End Results (SEER) database. Multivariate Cox regression analysis was used to determined prognostic factors of overall survival (OS) and cancer-specific survival (CSS), and two nomograms were constructed and validated by calibration plots, concordance index (C-index) and decision curve analysis (DCA). Additionally, 432 patients from the First Affiliated Hospital of Wenzhou Medical University were included as an external cohort. Kaplan-Meier curves were applied to further verify the clinical validity of the nomograms.

Results: Ten independent prognostic factors were identified to establish the nomograms. The C-indexes of the training and validation groups based on the OS nomogram were 0.759 and 0.760, higher than those of the tumor-node-metastasis (TNM) staging system (0.638 and 0.636, respectively). Calibration curves showed high consistency between predictions and observations. Better area under the receiver operator characteristic (ROC) curve (AUC) values and DCA were also obtained compared to the TNM system. The risk stratification based on the nomogram could distinguish patients with different survival risks.

Conclusions: We constructed and externally validated a population-based survival-predicting nomogram for PDAC patients aged ≥60 years. The new model could help clinicians personalize survival prediction and risk assessment.

Keywords: Pancreatic ductal adenocarcinoma (PDAC); nomogram; survival prediction; elderly patients; tumor-node-metastasis staging (TNM staging)

Submitted Jan 02, 2024. Accepted for publication May 07, 2024. Published online Jun 13, 2024.
doi: 10.21037/tcr-24-5
View this article at: https://dx.doi.org/10.21037/tcr-24-5

^ ORCID: 0000-0002-6806-7872.

Introduction

Pancreatic cancer (PC) is a highly aggressive malignant tumor characterized by metastatic susceptibility, poor therapeutic effect and poor prognosis (1,2). Early diagnosis is difficult, and as the disease progresses to advanced stages, most patients have no obvious symptoms. Due to its late-stage and poor prognosis, and difficulties in developing effective treatments, the mortality of the disease is increasing, and it is projected to become the second most common cause of cancer death in developed countries by 2040 (3). Surgical resection remains the only curative method for PC patients. However, the majority of patients were diagnosed at an advanced stage and only 20–30% had the opportunity to undergo surgical resection (4,5). Chemotherapy is the primary treatment option for most patients with metastatic PC, but the objective response rate of first-line chemotherapy is less than 50% (6,7). Immunotherapy, which has obtained satisfactory effects in other cancers, has not achieved desirable results in PC (8,9), mainly due to its immunosuppressive tumor microenvironment (10). The 5-year relative overall survival (OS) rate of the disease is approximately 11%, with a median survival time of less than 1 year (11).

Age is considered to be an independent prognostic factor for many cancers, including PC (12-14). Previous studies have shown that the clinical features and prognosis of elderly PC patients differ from those of younger patients (12,15,16). It is commonly believed that older patients are less tolerant to surgery, chemotherapy and radiation, leading to poorer adherence to anti-tumor treatment and increased side effects. Besides, aging is accompanied by cellular senescence, including homeostasis changes, protein and nuclear genome instability, which may be involved in the occurrence and development of tumors (17-19). Currently, the American Joint Committee on Cancer (AJCC) TNM (tumor-node-metastasis) staging system is widely used in clinical practice to predict prognoses and develop treatment plans (20). However, it only incorporates some pathological factors and ignores other potential variables, such as age, gender, obesity, smoking status, alcohol use, comorbidities and tumor differentiation etc. (21). Notably, survival can vary greatly among patients with the same TNM stage of disease (22). Thus, a more accurate and specific prediction model than AJCC staging is needed for prognostic analysis of elderly patients with PC.

Nomograms are a valuable tool to determine statistical prognostic models using different clinicopathological variables to produce probabilities of clinical outcomes for individual patients (23). Nomograms have been used in a variety of cancers, showing superior results when compared to the traditional AJCC staging system (24-26). Pancreatic ductal adenocarcinoma (PDAC), which accounts for the vast majority of PC, shows the lowest OS and worst prognosis in patients with PC (27). For patients with metastatic PDAC, the 5-year OS rate is less than 3% (28). Few studies have reported the clinical characteristics and prognosis of elderly patients with PDAC (12,29). As far as we know, there are no specific nomograms considering both OS and cancer-specific survival (CSS) for elderly PDAC patients. Zhong *et al.* developed a web-based prediction model for predicting OS in PC patients aged ≥65 years. However, the study included all pathological types of PC and the nomogram was not externally validated (12). Our study aimed to investigate the prognostic factors for OS and CSS in PDAC patients aged ≥60 years and further develop a population-based survival-predicting model with external validation. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-5/rc).

Highlight box

Key findings

- We successfully constructed and externally validated a reliable nomogram to predict survival in pancreatic ductal adenocarcinoma (PDAC) patients aged ≥60 years, which showed superiority over the traditional tumor-node-metastasis (TNM) staging system.

What is known, and what is new?

- Age is considered to be an independent factor affecting survival outcomes in patients with PDAC. The traditional TNM staging system only incorporates some pathological factors and ignores other potential variables, such as age, gender, tumor differentiation.
- A comprehensive nomogram including the TNM staging system was constructed to more accurately predict the prognosis of PDAC patients aged ≥60 years.

What is the implication, and what should change now?

- This new nomogram could help clinicians personalize survival prediction and risk assessment. Further prospective studies with larger sample sizes and more detailed clinical information are warranted to improve the accuracy and applicability of our model.

Methods

Patient selection

The Surveillance, Epidemiology, and End Results (SEER)

database is the largest publicly available cancer database in the United States and collects patient information including demographics, clinicopathological features, treatment regimen, and survival. We used SEER*Stat software (v 8.3.5) to identify PC patients in the database between 1975 and 2017. Patients with primary PDAC and aged ≥60 years were included using histological types [International Classification of Diseases for Oncology, Third Edition (ICD-O-3): 8140 and 8500] and from the corresponding locations [Site recode ICD-O-3/World Health Organization (WHO) 2008: pancreas]. The following baseline characteristics of PDAC patients were collected: age, gender, marital status, race, tumor location, tumor size, histology grade, liver metastasis, lung metastasis, bone metastasis, the 7th TNM stage (published in 2010), radiation, chemotherapy, surgery, vital status, cause of death and survival months. Patients with missing or incomplete information on the above variables were excluded. CSS was defined as the time interval between initial diagnosis of PC to death. OS was defined as the time from first diagnosis to death from any cause or data from the last follow-up.

We retrospectively gathered data from 432 PDAC patients aged ≥60 years in The First Affiliated Hospital of Wenzhou Medical University from 2007 to 2017 as an external validation cohort for this study. The inclusion and exclusion criteria for external validation cohort were the same as for internal cohort. We further collected information on independent prognostic variables based on the training cohort. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of The First Affiliated Hospital of Wenzhou Medical University (No. YS2022-241) and individual consent for this retrospective analysis was waived. The flow chart of our study is shown in Figure S1.

Nomogram development and statistical analyses

In this study, R software (version 3.4.2) was used to analyze the data. After rigorous screening, a total of 7,212 PDAC patients aged ≥60 years were included from the SEER database. These patients were randomly divided into a training cohort (n=5,052) and an internal validation cohort (n=2,160) at a ratio of 7:3. Statistically significance was considered for two-sided P values <0.05. Categorical data (including age) was shown as numbers and proportions, and chi-square test or Fisher exact test were used between subgroups. In the training group, univariable and multivariable cox proportional hazard regression analyses were used to determine the factors affecting CSS and OS. We constructed nomograms using prognostic factors identified in multivariate analysis and tested its ability to predict 1- and 2-year survival in PDAC patients aged ≥60 years through internal and external validation cohorts.

Calibration curves were plotted to show agreement between observations and estimated survival. The concordance index (C-index) and area under the receiver operator characteristic (ROC) curve (AUC) were used to evaluate the discriminatory ability of the nomogram. Decision curve analysis (DCA) was applied to evaluate the clinical utility of the nomogram, and the DCA curves were plotted to calculate the clinical net benefit rate (30). We divided patients into high and low-risk groups according to nomogram risk scores, the dividing point of which was derived from ROC curve. We used Kaplan-Meier analysis and log-rank tests to compare survival differences between high-risk and low-risk groups.

Results

Patient characteristics

Detailed demographic and clinicopathological information is listed in *Table 1*. In the training set, there were 2,285 (45.3%) patients aged 60–69 years, 2,566 (50.8%) females, 4,100 (81.2%) White, 3,087 (61.1%) married, and 4,527 (89.6%) insured patients. PDAC was most likely occurring in the head of pancreas (67.3%). Grade II (45.5%) was the most common degree of differentiation. The majority of patients were AJCC stage II (n=2,842, 56.3%). In terms of treatment, 2,881 cases (57.0%) underwent surgery, 3,259 cases (64.5%) underwent chemotherapy, and 1,180 cases (23.4%) underwent radiation. Among the distant metastases of PDAC, 72 cases (1.4%) had bone metastases, 959 cases (19.0%) had liver metastases, and 260 cases (5.1%) had lung metastases. Regarding tumor size, 2.1–4.0 cm accounted for 54.8%. As for the validation cohort, there were slightly more women [1,085 (50.2%)] than men [1,075 (49.8%)]. The most common tumor site was the head of the pancreas (67.7%), followed by the body (12.6%) and the tail (11.3%). As for tumor size, the median size (2.1–4 cm, 57.0%) was the most common, followed by large size (>4 cm, 32.4%) and small size (≤2 cm, 10.6%). There was no statistical significance in the distribution of variables between the two groups (P>0.05).

In addition, 432 patients from The First Affiliated

Table 1 Patient characteristics

Variables	Total (n=7,212)	Training cohort (n=5,052)	Validation cohort (n=2,160)	P
Age (years)				0.20
60–69	3,297 (45.7)	2,285 (45.3)	1,012 (46.9)	
70–79	2,681 (37.2)	1,912 (37.8)	769 (35.6)	
≥80	1,234 (17.1)	855 (16.9)	379 (17.5)	
Sex				0.66
Female	3,651 (50.6)	2,566 (50.8)	1,085 (50.2)	
Male	3,561 (49.4)	2,486 (49.2)	1,075 (49.8)	
Race				0.71
Black	732 (10.1)	519 (10.2)	213 (9.9)	
White	5,851 (81.1)	4,100 (81.2)	1,751 (81.1)	
Others	629 (8.8)	433 (8.6)	196 (9.0)	
Marital status				0.65
Married	4,419 (61.3)	3,087 (61.1)	1,332 (61.7)	
Unmarried/single	2,793 (38.7)	1,965 (38.9)	828 (38.3)	
Insurance				0.61
Insured	6,447 (89.4)	4,527 (89.6)	1,920 (88.9)	
Any medicaid	654 (9.1)	447 (8.8)	207 (9.6)	
Uninsured	111 (1.5)	78 (1.6)	33 (1.5)	
Location				0.71
Head	4,864 (67.4)	3,401 (67.3)	1,463 (67.7)	
Body	867 (12.0)	595 (11.8)	272 (12.6)	
Tail	879 (12.2)	634 (12.5)	245 (11.4)	
Pancreatic duct	41 (0.6)	28 (0.6)	13 (0.6)	
Other specified parts	104 (1.4)	75 (1.5)	29 (1.3)	
Overlapping lesion	457 (6.4)	319 (6.3)	138 (6.4)	
Grade				0.13
I	791 (11.0)	579 (11.5)	212 (9.8)	
II	3,314 (46.0)	2,300 (45.5)	1,014 (46.9)	
III	3,004 (41.7)	2,096 (41.5)	908 (42.0)	
IV	103 (1.3)	77 (1.5)	26 (1.2)	
AJCC TNM stage (7th)				0.88
I	581 (8.1)	412 (8.2)	169 (7.8)	
II	4,079 (56.6)	2,842 (56.3)	1,237 (57.3)	
III	652 (9.0)	459 (9.1)	193 (8.9)	
IV	1,900 (26.3)	1,339 (26.4)	561 (26.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=7,212)	Training cohort (n=5,052)	Validation cohort (n=2,160)	P
Surgery				0.27
No	3,069 (42.6)	2,171 (43.0)	898 (41.6)	
Yes	4,143 (57.4)	2,881 (57.0)	1,262 (58.4)	
Chemotherapy				0.47
No/unknown	2,579 (35.8)	1,793 (35.5)	786 (36.4)	
Yes	4,633 (64.2)	3,259 (64.5)	1,374 (63.6)	
Radiation				0.88
No/unknown	5,524 (76.6)	3,872 (76.6)	1,652 (76.5)	
Yes	1,688 (23.4)	1,180 (23.4)	508 (23.5)	
Bone metastasis				0.63
No	7,106 (98.5)	4,980 (98.6)	2,126 (98.4)	
Yes	106 (1.5)	72 (1.4)	34 (1.6)	
Liver metastasis				0.55
No	5,856 (81.2)	4,093 (81.0)	1,763 (81.6)	
Yes	1,356 (18.8)	959 (19.0)	397 (18.4)	
Lung metastasis				0.70
No	6,836 (94.8)	4,792 (94.9)	2,044 (94.6)	
Yes	376 (5.2)	260 (5.1)	116 (5.4)	
Size (cm)				0.22
≤2	774 (10.7)	546 (10.8)	228 (10.6)	
2.1–4	4,000 (55.5)	2,769 (54.8)	1,231 (57.0)	
>4	2,438 (33.8)	1,737 (34.4)	701 (32.4)	

Data are shown as n (%). AJCC, American Joint Committee for Cancer; TNM, tumor-node-metastasis.

Hospital of Wenzhou Medical University were also included (Table S1). Most patients (40.5%) were aged 70–79 years. The tumors were mostly at histologic grade III (n=173, 40.1%) and AJCC stage II (n=201, 46.5%). Among these patients, 229 (53.0%), 46 (10.6%) and 248 (57.4%) received surgery, radiation and chemotherapy, respectively. The liver was the most common site of metastasis (23.1%).

Independent prognostic factors for PDAC aged ≥60 years

First, we performed a univariate Cox proportional hazards regression analysis in the training cohort. Then, all the variables with P<0.05 were accessed into multivariate Cox proportional hazards regression analysis. Finally, age, grade, AJCC stage, chemotherapy, surgery, radiation, bone metastasis, liver metastasis, lung metastasis and tumor size were identified as independent prognostic factors for both OS and CSS. The results of univariate and multivariate analyses are shown in *Table 2*.

Nomogram construction for 1- and 2-year OS and CSS

Based on the significant and independent prognostic factors identified by the multivariate analysis, nomograms for predicting OS and CSS of PDAC patients aged ≥60 years were constructed (*Figure 1*). The nomograms showed that surgery was the most significant variable affecting the prognosis of patients, followed by chemotherapy, AJCC stage, tumor grade and size. Score each level of each variable on the nomogram. By adding the scores of the selected

Table 2 Univariate and multivariate analysis of survival in the training cohort

Variables	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Log-rank χ^2	P	HR (95% CI)	P	Log-rank χ^2	P	HR (95% CI)	P
Sex	0.000	0.98			0.124	0.73		
Female								
Male								
Age (years)	146.758	<0.001		<0.001	130.505	<0.001		<0.001
60–69			Reference				Reference	
70–79			1.203 (1.123–1.289)	<0.001			1.172 (1.092–1.258)	<0.001
≥80			1.342 (1.225–1.469)	<0.001			1.340 (1.220–1.471)	<0.001
Race	11.174	0.004		0.11	7.443	0.02		0.21
Black			Reference				Reference	
White			0.907 (0.820–1.005)	0.06			0.930 (0.836–1.034)	0.18
Others			0.867 (0.750–1.001)	0.052			0.875 (0.753–1.016)	0.08
Marital status	29.975	<0.001			19.199	<0.001		
Married			Reference				Reference	
Unmarried/single			1.037 (0.972–1.106)	0.27			1.014 (0.948–1.084)	0.69
Insurance	23.145	<0.001		0.39	12.789	0.002		0.76
Insured			Reference				Reference	
Any medicaid			1.077 (0.967–1.199)	0.18			1.036 (0.925–1.160)	0.54
Uninsured			0.980 (0.758–1.266)	0.88			0.947 (0.725–1.237)	0.69
Location	77.085	<0.001		0.06	83.348	0.01		0.07
Head			Reference				Reference	
Body			0.879 (0.796–0.970)	0.01			0.888 (0.803-0.983)	0.02
Tail			0.908 (0.822–1.002)	0.054			0.904 (0.817–1.001)	0.051
Pancreatic duct			0.919 (0.597–1.414)	0.70			0.883 (0.562–1.389)	0.59
Other specified parts			0.780 (0.606–1.003)	0.053			0.793 (0.613–1.025)	0.08
Overlapping lesion			0.963 (0.848–1.095)	0.57			0.971 (0.852–1.107)	0.66
Grade	176.820	<0.001		<0.001	177.768	<0.001		<0.001
I			Reference				Reference	
II			1.364 (1.225–1.518)	<0.001			1.399 (1.251–1.564)	<0.001
III			1.617 (1.251–2.090)	<0.001			1.620 (1.243–2.112)	<0.001
IV			1.763 (1.583–1.963)	<0.001			1.814 (1.622–2.029)	<0.001
AJCC TNM stage (7th)	1,213.047	<0.001		<0.001	1,260.683	<0.001		<0.001
I			Reference				Reference	
II			1.473 (1.254–1.730)	<0.001			1.566 (1.324–1.853)	<0.001
III			1.536 (1.350–1.749)	<0.001			1.622 (1.414–1.860)	<0.001
IV			1.943 (1.638–2.305)	<0.001			2.077 (1.739–2.482)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Overall survival				Cancer-specific survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Log-rank χ^2	P	HR (95% CI)	P	Log-rank χ^2	P	HR (95% CI)	P
Surgery	1,524.697	<0.001			1,552.292	<0.001		
No			Reference				Reference	
Yes			0.377 (0.346–0.411)	<0.001			0.363 (0.332–0.397)	<0.001
Chemotherapy	596.701	<0.001			509.359	<0.001		
No/unknown			Reference				Reference	
Yes			0.456 (0.425–0.489)	<0.001			0.461 (0.429–0.495)	<0.001
Radiation	221.638	<0.001			194.634	<0.001		
No/unknown			Reference				Reference	
Yes			0.839 (0.774–0.910)	<0.001			0.856 (0.787–0.930)	<0.001
Bone metastasis	69.207	<0.001			75.170	<0.001		
No			Reference				Reference	
Yes			1.389 (1.082–1.782)	0.010			1.412 (1.098–1.816)	0.007
Liver metastasis	970.627	<0.001			1,006.967	<0.001		
No			Reference				Reference	
Yes			1.262 (1.112–1.432)	<0.001			1.269 (1.116–1.443)	<0.001
Lung metastasis	269.349	<0.001			276.559	<0.001		
No			Reference				Reference	
Yes			1.170 (1.016–1.348)	0.03			1.173 (1.016–1.354)	0.03
Size (cm)	304.206	<0.001		<0.001	300.196	<0.001		<0.001
≤2			Reference				Reference	
2.1–4			1.500 (1.338–1.681)	<0.001			1.470 (1.307–1.653)	<0.001
>4			1.837 (1.627–2.074)	<0.001			1.808 (1.595–2.049)	<0.001

AJCC, American Joint Committee for Cancer; TNM, tumor-node-metastasis; HR, hazard ratio; CI, confidence interval.

variables, the nomograms could be used to predict 1- and 2-year OS and CSS in PDAC patients aged ≥60 years.

Calibration and internal validation

The calibration plots for the training cohort and the internal validation cohort used to predict OS showed good agreement between the actual observation and nomogram predicted survival (*Figure 2*). A similar result for CSS was demonstrated in Figure S2. In the training cohort, nomograms of OS and CSS showed strong prediction capabilities, with C-indexes of 0.759 [95% confidence interval (CI): 0.751–0.767] and 0.760 (95% CI: 0.752–0.768), respectively. Additionally, the established nomograms demonstrated higher values of C-indexes compared with the 7th TNM stage system, indicating improved discriminatory ability in predicting OS and CSS (*Table 3*). For the internal validation cohort, similar results were observed in both OS and CSS nomograms (*Table 3*).

Comparison of the nomogram and 7th TNM staging system

The AUC values of the OS nomogram were superior to the 7th TNM staging in both the training set (1-year: 0.829 *vs.* 0.678, 2-year: 0.802 *vs.* 0.679) and internal validation set (1-year: 0.821 *vs.* 0.678, 2-year: 0.809 *vs.* 0.681) (*Figure 3*, *Table 4*). For the CSS nomogram, the AUC values also outperformed the traditional TNM model (Figure S3, *Table 4*). The DCAs are commonly used to evaluate the

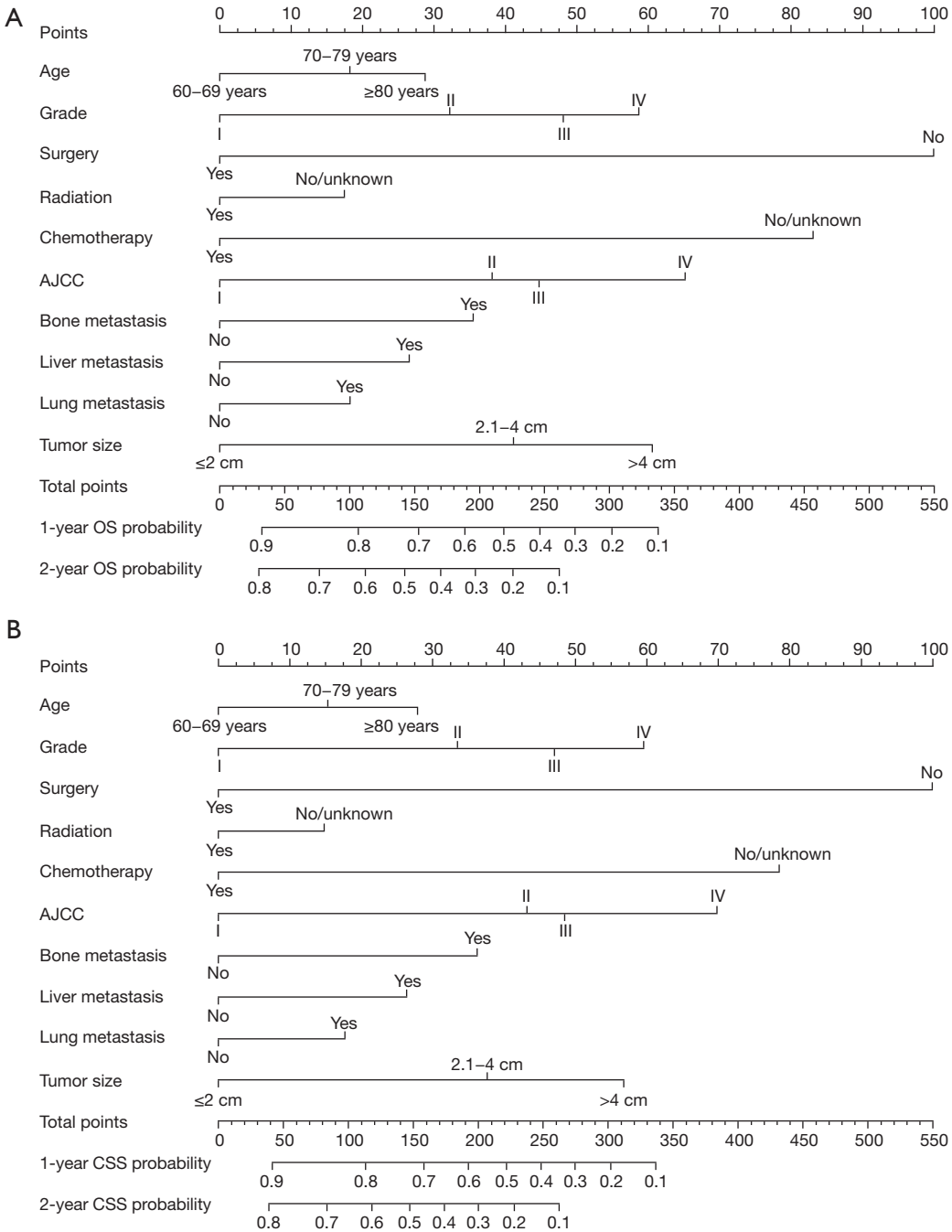

Figure 1 Nomogram predicting 1- and 2-year OS (A) and CSS (B) of patients with pancreatic ductal adenocarcinoma. AJCC, American Joint Committee for Cancer; OS, overall survival; CSS, cancer-specific survival.

clinical value of OS and CSS nomograms. As shown in *Figure 4* and Figure S4, comparisons between nomograms and 7th TNM staging system showed that the net benefit of nomograms consistently improved, indicating that our nomograms were superior to the traditional TNM stage in predicting OS and CSS in PDAC patients aged ≥60 years.

External validation of nomogram

The established nomograms were externally validated to

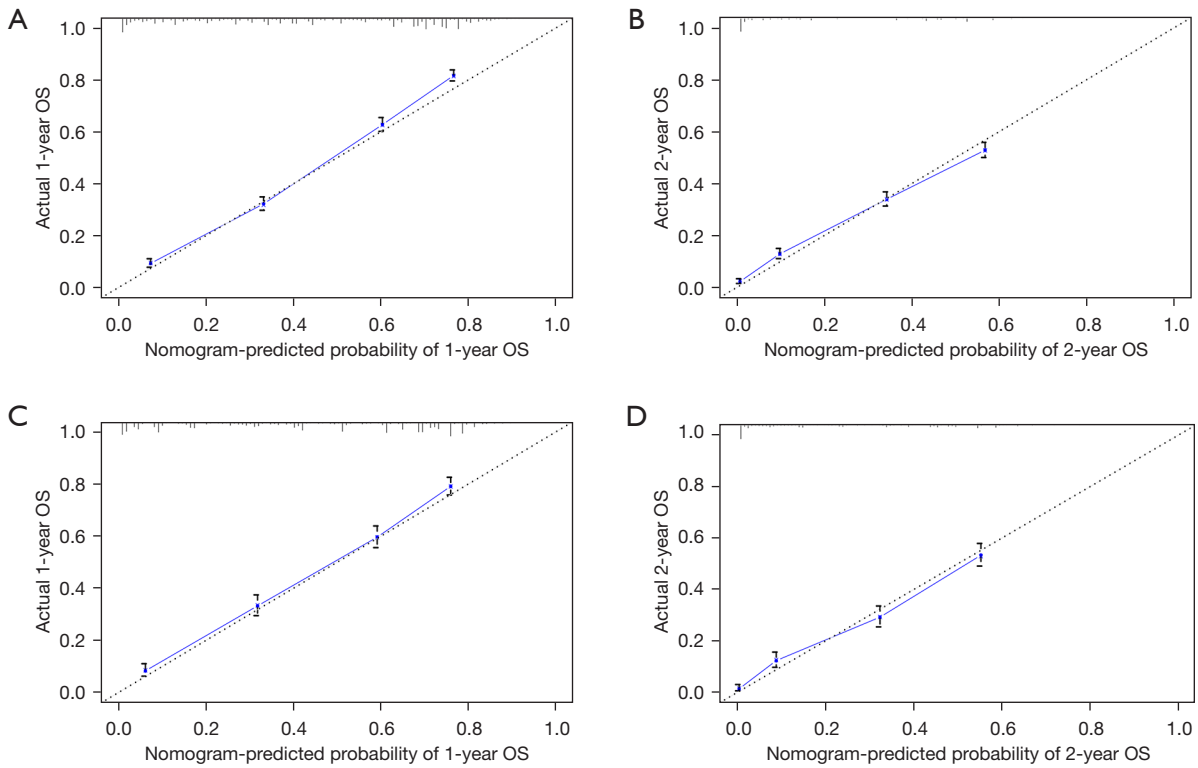

Figure 2 Calibration plots of the nomogram for 1- and 2-year OS prediction of the training cohort (A,B) and internal validation cohort (C,D). OS, overall survival.

Table 3 C-indexes for the nomograms and TNM stage system in PDAC patients aged ≥60 years

Patients	Overall survival		Cancer-specific survival	
	C-index	P value	C-index	P value
Training cohort		<0.001		<0.001
Nomogram	0.759 (0.751–0.767)		0.760 (0.752–0.768)	
7th TNM stage	0.638 (0.630–0.646)		0.644 (0.636–0.652)	
Internal validation cohort		<0.001		<0.001
Nomogram	0.760 (0.748–0.772)		0.761 (0.749–0.773)	
7th TNM stage	0.636 (0.622–0.650)		0.639 (0.625–0.653)	

TNM, tumor-node-metastasis; C-index, concordance index; PDAC, pancreatic ductal adenocarcinoma.

further illustrate the clinical application. The C-indexes of OS and CSS nomograms were 0.800 (95% CI: 0.773–0.827) and 0.799 (95% CI: 0.771–0.826), respectively, which were both higher than those of the 7th TNM staging system. Also, the AUC values of the nomograms for predicting 1- and 2-year survival were 0.843 and 0.860, and 0.849 and 0.862 for OS and CSS, respectively, indicating a high predictive ability in external validation (*Figure 5*). The calibration curves (*Figure 6*) still showed that the nomograms had good agreement. Additionally, we developed a risk stratification system according to patients' total scores on the nomogram. The Kaplan-Meier curves demonstrated that there were significant differences in survival between high and low risk groups (P<0.001) (*Figure 7*).

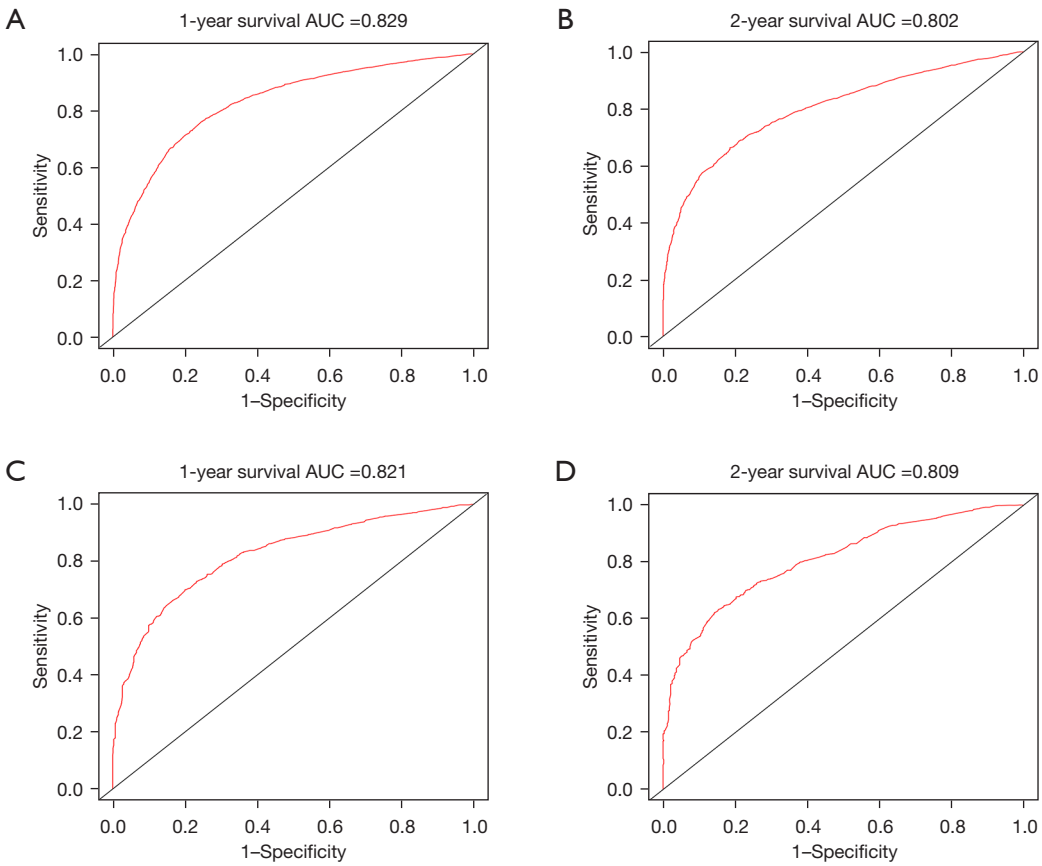

Figure 3 The ROC curves of the nomograms for 1- and 2-year OS prediction of the training cohort (A,B) and internal validation cohort (C,D). AUC, area under the curve; ROC, receiver operating characteristic; OS, overall survival.

Table 4 Comparison of AUC values between nomograms and TNM stage system in PDAC patients aged ≥60 years

Survival	Training cohort		Internal validation cohort	
	1-year survival	2-year survival	1-year survival	2-year survival
Overall survival				
Nomogram	0.829	0.802	0.821	0.809
7th TNM stage	0.678	0.679	0.678	0.681
Cancer-specific survival				
Nomogram	0.834	0.804	0.825	0.805
7th TNM stage	0.685	0.686	0.681	0.679

AUC, area under the curve; TNM, tumor-node-metastasis; PDAC, pancreatic ductal adenocarcinoma.

Discussion

PDAC accounts for approximately 90% of all pancreatic tumors and is usually diagnosed at a late stage, with systemic therapy being the primary treatment. Chemotherapy, which is now increasingly being used as a neoadjuvant therapy, has evolved to improve survival. The growing use of genomic testing in advanced PC has led to a better understanding of its biology, allowing doctors to consider potential targeted treatment (2,31). Despite the development of

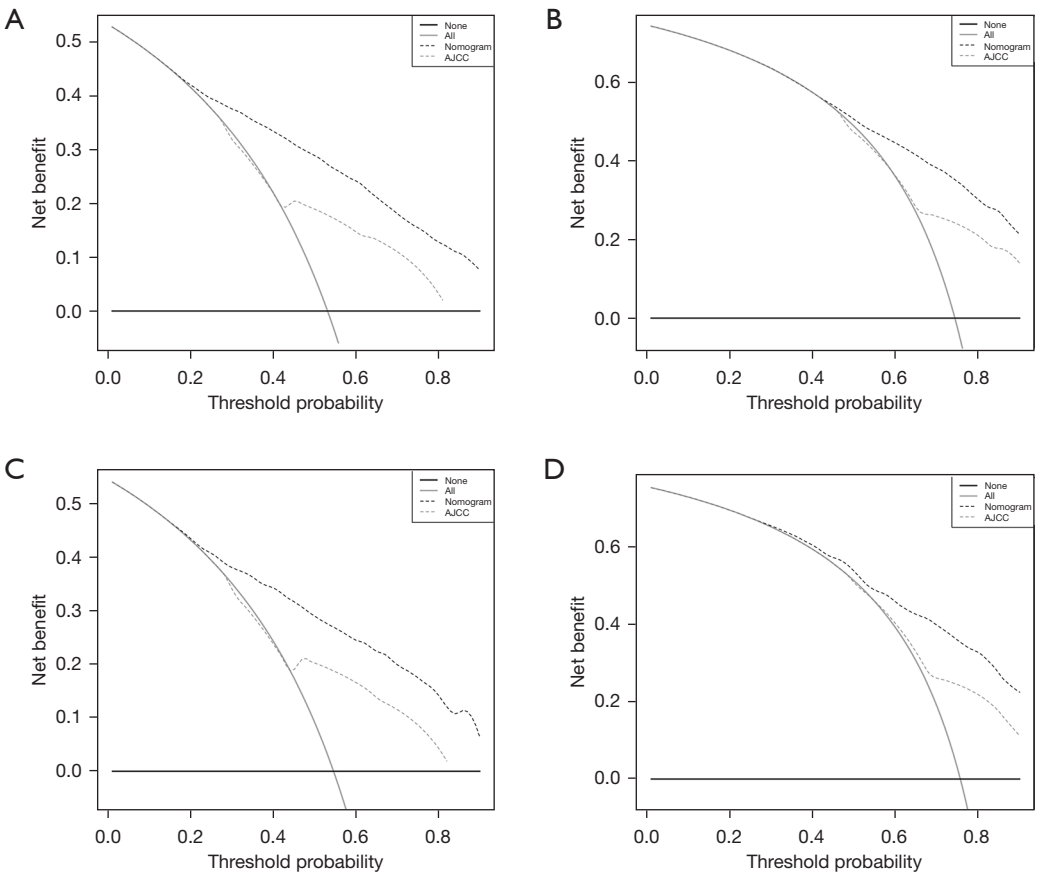

Figure 4 DCA of the nomogram and 7th AJCC TNM staging system for 1-year (A,C) and 2-year (B,D) overall survival in the training cohort (A,B) and internal validation cohort (C,D). AJCC, American Joint Committee for Cancer; DCA, decision curve analyses; TNM, tumor-node-metastasis.

novel therapies, survival remains limited, usually of less than 1 year (32). Many studies have shown that age is an independent variable affecting OS in PDAC patients (26,33-35). Since the clinical features and prognosis of elderly PDAC patients are different from those of younger patients (12,15,16), it is not accurate to rely solely on the traditional stage systems to estimate the prognosis of these patients. In the current study, we constructed a nomogram model based on a combination of independent prognostic factors to predict survival in PDAC patients aged ≥60 years. The new nomogram included ten variables including age, grade, AJCC staging, chemotherapy, surgery, radiation, lung metastases, bone metastases, liver metastases and tumor size, which could comprehensively predict survival prognosis and fill the gap in applying this model in elderly PDAC.

In our study, the majority of PDAC patients were white, 60–69 years old. Most tumors were located in the head of the pancreas. The majority of patients were in AJCC stage II with histological grade II and III. More than half of the patients were treated with chemotherapy and surgery. These were some of the disease characteristics for PDAC patients aged ≥60 years. Additionally, ten independent prognostic variables were identified for OS and CSS, which are in accordance with previous studies (12,15,35,36). Our model showed that surgery had the greatest impact on OS and CSS, followed by chemotherapy, AJCC stage and grade. Consistent with our findings, Zhong *et al.* established a prediction model for OS in elderly PC patients, in which surgery contributed the most to the final risk score (12). At present, surgery is usually considered the dominant modality in PDAC treatment. Over the past few decades, surgery for PC has become safer and the risk of postoperative mortality has dropped to 3% (37). Even in stage IV patients, some patients with distant isolated metastases treated

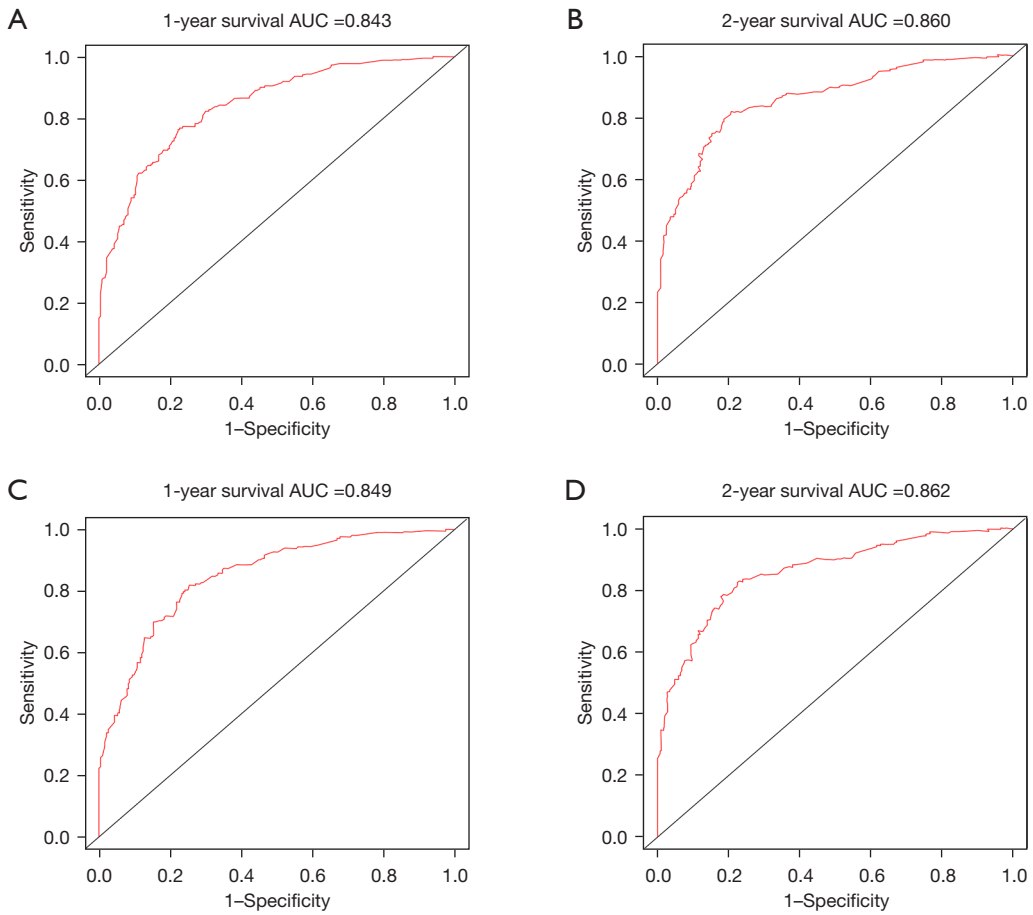

Figure 5 The ROC curves of the nomograms for 1- and 2-year OS (A,B) and CSS (C,D) prediction in external validation cohort. AUC, area under the curve; ROC, receiver operating characteristic; OS, overall survival; CSS, cancer-specific survival.

with neoadjuvant chemotherapy may undergo surgical evaluation after tumor shrinkage (38). However, suitability of patient for surgery is also dependent upon patient's health condition and the presence of comorbidities. We were unable to take these factors into account due to the lack of information in the SEER database. Future studies with more comprehensive data will be conducted to address these issues. Chemotherapy is considered to be the standard treatment for resected PDAC and primary first-line treatment for metastatic PC (39,40). Despite poor tolerance and compliance of chemotherapy in elderly patients, more than half of the patients in our study received chemotherapy, and its impact on OS and CSS was even greater than AJCC staging. Tumor grade or AJCC TNM staging system is a routine method used by physicians to assess cancer prognosis and select treatment strategies, but remains inaccurate due to its relative heterogeneity (41). Consistent with our study, several studies also attempted to combine these factors with other prognostic variables, thereby improving the predictive ability of their models (15,42).

In addition to the abovementioned factors, tumor size was also proven to be a significant parameter and included in our prognostic model, which is in accordance with other similar studies (25,43). The liver is the most common site of metastasis for PC, followed by the lungs. However, bone metastases are as rare as brain metastases (44,45). Yao *et al.* (46) found that liver and bone metastases were not only risk factors for lung metastasis of PC, but also independent prognostic factors for OS in these patients. Our study also found that liver and bone metastases significantly affected the prognosis of PDAC patients aged ≥60 years. Therefore, clinicians should be aware of screening for metastases at these sites to accurately assess prognosis.

In our study, the nomograms were constructed with

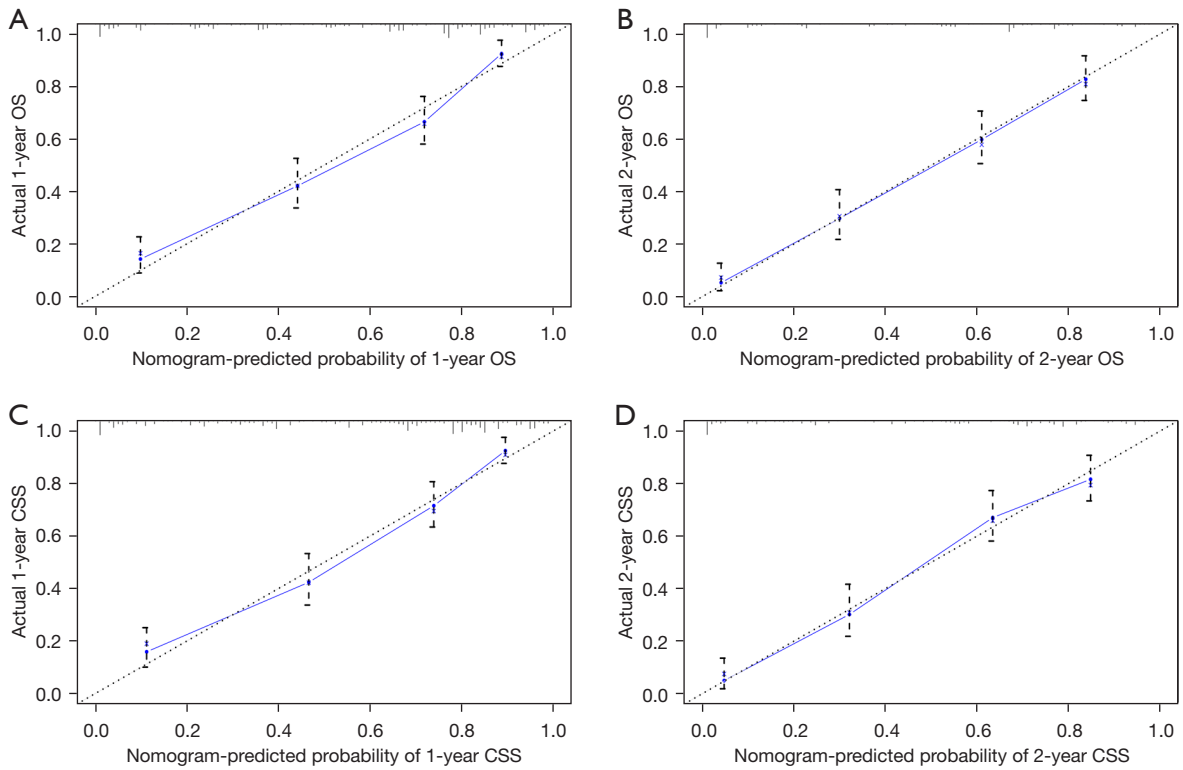

Figure 6 Calibration plots of the nomogram for 1- and 2-year OS (A,B) and CSS (C,D) prediction in external validation cohort. OS, overall survival; CSS, cancer-specific survival.

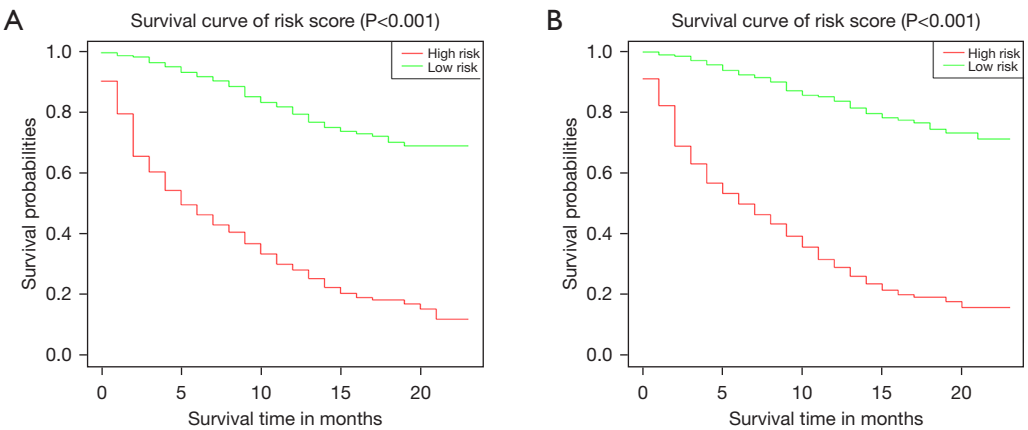

Figure 7 Kaplan-Meier curves of OS (A) and CSS (B) to test the risk stratification system in the external validation cohort. OS, overall survival; CSS, cancer-specific survival.

a large sample size from the SEER database, which guaranteed the reliability and stability of the results. The calibration plots showed that the 1- and 2-year survival probabilities predicted by nomograms were in good agreement with the actual observation. The C-indexes and AUC values of our nomograms were higher than those of the 7th AJCC staging system, indicating better discriminatory power to predict OS and CSS. Moreover, our model still demonstrated relatively higher C-index and AUC value in the external validation cohort, compared to

the elderly PC nomogram data reported by Zhong *et al.* (12) (C-index: 0.800 *vs.* 0.797, AUC: 0.843 *vs.* 0.828). The results of DCA analyses further proved that our nomograms were superior to the AJCC staging system in terms of clinical application. Finally, we applied one Chinese center to externally verify the nomograms. Kaplan-Meier curves showed significant differences in survival of patients in the high and low risk groups. As far as we know, this is the first nomogram based on a large multicenter dataset and an external validation cohort to effectively predict prognosis in PDAC patients aged ≥60 years. The nomograms, which consist of a few easily obtained variables, can be used to estimate the individualized survival probabilities and guide personalized treatment for elderly patients with PDAC.

There were several limitations in our study. First, it was a retrospective study with inevitable selection bias. Second, detailed information on radiation, chemotherapy, targeted therapy and surgical methods was incompletely recorded. In addition, other potential risk factors, such as family history, comorbidities, alcohol consumption, obesity or smoking, were also difficult to obtain from the SEER database, and these factors might confound the actual association. Finally, the sample size of external validation cohort was small, so future multi-center prospective studies should be conducted to further increase the number of cases, so as to improve the accuracy and reliability of the prediction model.

Conclusions

We established and externally validated a reliable nomogram specifically for predicting 1- and 2-year survival in PDAC patients aged ≥60 years, which showed superiority over the traditional TNM staging system. This new nomogram could help clinicians personalize survival prediction and risk assessment. Further prospective studies with larger sample sizes and more detailed clinical information are warranted to improve the accuracy and applicability of our model.

Acknowledgments

Funding: This work was supported by grants from Basic Public Welfare Research Program of Zhejiang Province (No. LQ21C080002).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-5/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-5/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-5/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-5/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of the First Affiliated Hospital of Wenzhou Medical University (No. YS2022-241) and individual consent for this retrospective analysis was waived.

References

1. Barros AG, Pulido CF, Machado M, et al. Treatment optimization of locally advanced and metastatic pancreatic cancer (Review). Int J Oncol 2021;59:110.
2. Kolbeinsson HM, Chandana S, Wright GP, et al. Pancreatic Cancer: A Review of Current Treatment and Novel Therapies. J Invest Surg 2023;36:2129884.
3. Rahib L, Wehner MR, Matrisian LM, et al. Estimated Projection of US Cancer Incidence and Death to 2040. JAMA Netw Open 2021;4:e214708.
4. Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362:1605-17.
5. Hartwig W, Hackert T, Hinz U, et al. Pancreatic cancer surgery in the new millennium: better prediction of

outcome. Ann Surg 2011;254:311-9.
6. Ansari D, Tingstedt B, Andersson B, et al. Pancreatic cancer: yesterday, today and tomorrow. Future Oncol 2016;12:1929-46.
7. Ramanathan RK, McDonough SL, Philip PA, et al. Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313. J Clin Oncol 2019;37:1062-9.
8. Adams S, Schmid P, Rugo HS, et al. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study. Ann Oncol 2019;30:397-404.
9. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
10. O'Reilly EM, Oh DY, Dhani N, et al. Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial. JAMA Oncol 2019;5:1431-8.
11. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
12. Zhong J, Liao X, Peng S, et al. A Visualized Dynamic Prediction Model for Overall Survival in Elderly Patients With Pancreatic Cancer for Smart Medical Services. Front Public Health 2022;10:885624.
13. Zhang W, Sun B. Impact of age on the survival of patients with liver cancer: an analysis of 27,255 patients in the SEER database. Oncotarget 2015;6:633-41.
14. Pettersson A, Robinson D, Garmo H, et al. Age at diagnosis and prostate cancer treatment and prognosis: a population-based cohort study. Ann Oncol 2018;29:377-85.
15. Shi M, Zhou B, Yang SP. Nomograms for predicting overall survival and cancer-specific survival in young patients with pancreatic cancer in the US based on the SEER database. PeerJ 2020;8:e8958.
16. Ansari D, Althini C, Ohlsson H, et al. Early-onset pancreatic cancer: a population-based study using the SEER registry. Langenbecks Arch Surg 2019;404:565-71.
17. Hartl FU. Cellular Homeostasis and Aging. Annu Rev Biochem 2016;85:1-4.
18. Soultoukis GA, Partridge L. Dietary Protein, Metabolism, and Aging. Annu Rev Biochem 2016;85:5-34.
19. Niedernhofer LJ, Gurkar AU, Wang Y, et al. Nuclear Genomic Instability and Aging. Annu Rev Biochem 2018;87:295-322.
20. Lim W, Ridge CA, Nicholson AG, et al. The 8(th) lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. Quant Imaging Med Surg 2018;8:709-18.
21. Park W, Chawla A, O'Reilly EM. Pancreatic Cancer: A Review. JAMA 2021;326:851-62.
22. Jouffret L, Turrini O, Ewald J, et al. Long-term survivors after pancreatectomy for cancer: the TNM classification is outdated. ANZ J Surg 2015;85:860-4.
23. Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015;16:e173-80.
24. Ren C, Ma Y, Jin J, et al. Development and external validation of a dynamic nomogram to predict the survival for adenosquamous carcinoma of the pancreas. Front Oncol 2022;12:927107.
25. He C, Sun S, Zhang Y, et al. Score for the Overall Survival Probability of Patients With Pancreatic Adenocarcinoma of the Body and Tail After Surgery: A Novel Nomogram-Based Risk Assessment. Front Oncol 2020;10:590.
26. Kang JS, Mok L, Heo JS, et al. Development and External Validation of Survival Prediction Model for Pancreatic Cancer Using Two Nationwide Databases: Surveillance, Epidemiology and End Results (SEER) and Korea Tumor Registry System-Biliary Pancreas (KOTUS-BP). Gut Liver 2021;15:912-21.
27. Zhang W, Ji L, Wang X, et al. Nomogram Predicts Risk and Prognostic Factors for Bone Metastasis of Pancreatic Cancer: A Population-Based Analysis. Front Endocrinol (Lausanne) 2022;12:752176.
28. Grossberg AJ, Chu LC, Deig CR, et al. Multidisciplinary standards of care and recent progress in pancreatic ductal adenocarcinoma. CA Cancer J Clin 2020;70:375-403.
29. Dai D, Wang Y, Hu X, et al. Prognostic analysis of very early onset pancreatic cancer: a population-based analysis. PeerJ 2020;8:e8412.
30. Van Calster B, Wynants L, Verbeek JFM, et al. Reporting and Interpreting Decision Curve Analysis: A Guide for Investigators. Eur Urol 2018;74:796-804.
31. Buckley CW, O'Reilly EM. Next-generation therapies for pancreatic cancer. Expert Rev Gastroenterol Hepatol 2024;18:55-72.
32. Singh RR, O'Reilly EM. New Treatment Strategies for Metastatic Pancreatic Ductal Adenocarcinoma. Drugs 2020;80:647-69.
33. He C, Zhang Y, Cai Z, et al. Overall survival and cancer-specific survival in patients with surgically resected pancreatic head adenocarcinoma: A competing risk

nomogram analysis. J Cancer 2018;9:3156-67.
34. Shao W, Lu Z, Xu J, et al. Effects of Total Pancreatectomy on Survival of Patients With Pancreatic Ductal Adenocarcinoma: A Population-Based Study. Front Surg 2021;8:804785.
35. Li Y, Tian M, Zhou Y, et al. A novel risk-scoring system conducing to chemotherapy decision for patients with pancreatic ductal adenocarcinoma after pancreatectomy. J Cancer 2021;12:4433-42.
36. Zhang W, Ji L, Zhong X, et al. Two Novel Nomograms Predicting the Risk and Prognosis of Pancreatic Cancer Patients With Lung Metastases: A Population-Based Study. Front Public Health 2022;10:884349.
37. Zhao Z, Liu W. Pancreatic Cancer: A Review of Risk Factors, Diagnosis, and Treatment. Technol Cancer Res Treat 2020;19:1533033820962117.
38. Strobel O, Neoptolemos J, Jäger D, et al. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol 2019;16:11-26.
39. De Dosso S, Siebenhüner AR, Winder T, et al. Treatment landscape of metastatic pancreatic cancer. Cancer Treat Rev 2021;96:102180.
40. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. JAMA 2012;308:147-56.
41. Diwakarla C, Hannan K, Hein N, et al. Advanced pancreatic ductal adenocarcinoma - Complexities of treatment and emerging therapeutic options. World J Gastroenterol 2017;23:2276-85.
42. Li W, Wang W, Yao L, et al. Nomogram for Predicting Distant Metastasis of Pancreatic Ductal Adenocarcinoma: A SEER-Based Population Study. Curr Oncol 2022;29:8146-59.
43. He C, Huang X, Zhang Y, et al. A Novel Prediction Tool Based on Large Cohorts to Determine the Cancer-Specific Survival Probability of Patients With Locally Advanced Pancreatic Cancer After Irreversible Electroporation Treatment. Front Oncol 2020;10:952.
44. Houg DS, Bijlsma MF. The hepatic pre-metastatic niche in pancreatic ductal adenocarcinoma. Mol Cancer 2018;17:95.
45. Luu AM, Künzli B, Hoehn P, et al. Prognostic value and impact of cerebral metastases in pancreatic cancer. Acta Chir Belg 2020;120:30-4.
46. Yao ZX, Tu JH, Zhou B, et al. Risk factors and survival prediction of pancreatic cancer with lung metastases: A population-based study. Front Oncol 2022;12:952531.

Cite this article as: Zheng B, Ding G, Lu G, Li L. Development and external validation of a prognostic nomogram to predict survival in patients aged ≥60 years with pancreatic ductal adenocarcinoma. Transl Cancer Res 2024;13(6):2751-2766. doi: 10.21037/tcr-24-5

