

RESEARCH

Open Access



Clinical characteristics and survival prediction of surgical patients with invasive pancreatic cystic neoplasm: a large retrospective study over two decades

Yanjing Song¹, Zhe Li¹, Hongyuan Cui¹, Jingyong Xu¹ and Jinghai Song^{1*}

Abstract

Purposes Invasive pancreatic cystic neoplasms (iPCNs) are an uncommon and biologically heterogeneous group of malignant neoplasms. We aimed to investigate the clinicopathological characteristics of iPCN patients and to develop nomograms for individual survival prediction after radical surgery.

Methods Data of patients diagnosed with iPCN and pancreatic ductal adenocarcinoma (PDAC) between 2000 and 2018 from the SEER database were retrieved. The differences in clinical outcomes were evaluated using the Kaplan–Meier analysis. Nomograms were proposed based on the Cox regression model and internally validated by C-index, area under the curve (AUC) value, and calibration plot.

Results A total of 7777 iPCN patients and 154,336 PDAC patients were enrolled. Most neoplasms were advanced, with 63.1% at stage IV. The 3-year overall survival (OS) and cancer-specific survival (CSS) rates in surgical patients were as follows: 45.7% and 50.1% for invasive intraductal papillary mucinous neoplasm (IPMN), 54.8% and 59.3% for invasive mucinous cystic neoplasm (MCN), 97.8% and 98.2% for invasive solid pseudopapillary neoplasm (SPN), 88.9% and 88.9% for invasive serous cystic neoplasm (SCN), and 27.3% and 30.5% for PDAC. Subgroup analyses showed no clinical benefit from chemotherapy or radiotherapy in lymph node-negative iPCN patients who underwent surgery. The following variables associated with OS and CSS were identified: age, race, chemotherapy, radiotherapy, histologic type, pathological grade, regional nodes examined, and T, N, and M stage. The nomograms had good discrimination and calibration by internal validation, with an AUC value of 0.800 for 3-year OS and 0.814 for 3-year CSS.

Conclusion Our study showed that the prognosis of iPCN patients was significantly better than PDAC patients. The proposed nomograms demonstrated substantially better discrimination and calibration.

Keywords Pancreatic cystic neoplasms (PCN), Overall survival (OS), Cancer-specific survival (CSS), Prognostic factors, Nomogram

Introduction

Pancreatic cystic neoplasm (PCN) is a lesion with heterogeneous proliferation of pancreatic epithelial tissue, characterized by unilocular or multilocular cavity formation due to retention of secretion. According to the 2019 WHO classification of pancreatic tumors [1], there are four main types of PCN: intraductal papillary mucinous

*Correspondence:

Jinghai Song
jhaisong2003@126.com

¹ Department of General Surgery, Department of Hepato-Bilio-Pancreatic Surgery, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, NO. 1 DaHua Road, Dong Dan, Beijing 100730, People's Republic of China



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystic neoplasm (SCN), solid pseudopapillary neoplasm (SPN), and other rare types, such as cystic neuroendocrine tumors (cNET), most of which encompasses variable grades of lesions ranging from benign neoplasms to invasive cancer (referred to as invasive PCN). Furthermore, PCN can also be categorized into serous or mucinous neoplasms, the prognosis of which is completely different [2].

With the development of medical imaging, the rate of detection of PCN has greatly increased. PCN were detected in up to 49.1% of tested individuals using magnetic resonance cholangiopancreatography [3]. IPMN is the most common PCN, followed by MCN, SCN, and SPN, all of which account for approximately 90% of cystic tumors of the pancreas [4]. The malignant potential varies between PCN types, and the prognosis is diverse. Previous studies suggested that SCNs are generally benign [5], whereas IPMN, MCN, and SPN are precancerous lesions that require long-term monitoring. In several studies, approximately 11–30% of side-branch (SB)-IPMN and 10–39% of MCN developed into advanced neoplasia (high-grade dysplasia or invasive cancer) [2], implying inaccuracies in the choice of operative indication, and more in-depth research on the clinicopathological features of PCN is needed. Currently, reliable survival statistics regarding prognosis and risk factors contributing to differences between types remain uncertain. The American Joint Committee on Cancer (AJCC) TNM staging system, a widely used criterion for staging patients with invasive PCN (iPCN), analogous to pancreatic ductal adenocarcinoma (PDAC), may not meet the need for accurate survival prediction for an individual patient with particular characteristics.

In this retrospective analysis, we comprehensively investigated the clinicopathological characteristics of patients with various iPCN types from the US Surveillance, Epidemiology, and End Results (SEER) database to evaluate survival differences among pathological types, including PDAC. We subsequently created and validated new nomograms for predicting overall survival (OS) and cancer-specific survival (CSS) of surgical iPCN patients based on the identified prognostic factors, and compared the predictive values with the AJCC 8th TNM staging system. Finally, we aimed to offer a clinically practical method to guide physicians in the postoperative management of surgical patients with iPCN.

Method

Patients and data collection

Data of patients diagnosed with pancreatic cancer (PC) between 2000 and 2018 from the SEER-18 database were retrieved using the National Cancer Institute's SEER*Stat

software (version 8.3.9.2). According to the ICD-O-3, neoplasms were pathologically confirmed using the following topography and morphology codes: C25.0–C25.9 for PC; 8050/3, 8260/3, 8450/3, 8453/3, 8471/3, 8480/3, 8481/3, and 8503/3 for invasive IPMN (iIPMN), also defined as IPMN with an associated invasive carcinoma; 8440/3 and 8470/3 for invasive MCN (iMCN), also defined as MCN with an associated invasive carcinoma; 8452/3 for invasive SPN (iSPN); 8441/3 and 8460/3 for invasive SCN (iSCN), also defined as serous cystadenocarcinoma; and 8010/3, 8140/3, and 8500/3 for PDAC. In our study, patients with available information on survival time who were diagnosed with iPCN or PDAC by positive histology from 2000 to 2018 were included, and the following patients were excluded when performing statistical analysis: (a) patients who were younger than 19 years or older than 99 years; (b) patients whose postoperative survival time was less than one month (to avoid the impact of early severe complications); (c) patients with incomplete information on the primary site, surgery, radiation, chemotherapy, pathological grade, cancer stage data, or follow-up data.

Demographic and clinicopathological data such as race, sex, age, year of diagnosis, primary site, histologic type, pathological grade (using a four-grade system of differentiation), surgery, chemotherapy, radiotherapy, tumor size, extent of disease, number of regional nodes examined, TNM stage, and follow-up information were collected. Since the SEER database only provided the stages based on the seventh or earlier edition of the AJCC staging system for patients diagnosed before 2017, we utilized the information from the collaborative stage data collection system in SEER database to re-stratify these patients according to TNM stage, as defined by the AJCC 8th edition, into the following groups: T1 (0–20mm), T2 (21–40mm), T3 (>40mm), T4 (the celiac axis, superior mesenteric artery, or common hepatic artery involved), N0, N1 (1–3), N2 (>3), M0, and M1. Some lymph node locations identified as regional nodes by AJCC 6th staging were reclassified as distant nodes by the 8th staging and labeled M1, such as celiac axis and splenic nodes for pancreatic head cancer. Treatment and operative details included the surgical approach (patients who underwent partial pancreatectomy, local or partial pancreatectomy, and duodenectomy with or without partial gastrectomy, total pancreatectomy, total pancreatectomy, and subtotal gastrectomy or duodenectomy, extended pancreatoduodenectomy, pancreatectomy-not otherwise specified (NOS) and surgery-NOS were classified as the surgery group, while others were classified as the non-surgical group), as well as information on adjuvant chemotherapy and radiotherapy. Survival information was retrieved using the phrases “vital status,” “SEER other cause of

death classification,” “SEER cause-specific death classification,” and “survival months.” The primary outcomes of interest were OS and CSS. OS was defined as the time from the date of diagnosis to death from any cause, and CSS was defined as the time from the date of diagnosis to death from pancreatic cancer.

Statistical analysis

Categorical variables are presented as whole numbers or proportions and analyzed using the chi-square test. Survival estimates were generated using the Kaplan–Meier method, and the differences in OS and CSS among groups were evaluated using the log-rank test. To identify potential risk factors for survival, multivariate regression analyses were performed using a Cox proportional hazard model with backward stepwise selection using the Akaike information criterion (AIC) and were reported as the Hazard ratio (HR) with 95% confidence interval (CI). To manage confounding variables associated with prognosis between iIPMN and PDAC patients, a 1:2 nearest neighbor propensity score matching (PSM) with a caliper of 0.02 was performed. Identified factors were included in the nomograms to predict the 1-, 2-, and 3-year OS and CSS rates of iPCN patients who underwent radical surgery. We used restricted cubic splines (RCS) with five knots to flexibly model the association between continuous predictors and death risks. Concordance statistic (C-index) and receiver operating characteristic (ROC) curve were used to evaluate the discriminative ability of the nomogram. A calibration plot was used to evaluate the calibrating ability, and bootstrapping method (1000 repetitions) was used for internal validation of the nomogram. Decision curve analysis (DCA) was performed to compare clinical benefits and usability between the nomogram and TNM staging system. In addition, Kaplan–Meier plots were carried out on the tertiles of patients stratified by the total points predicted by the nomograms using X-tile software (version 3.6.1). All statistical analyses were performed using R software (version 4.1.0) and RStudio (version 2021.09.0+351). A two-sided $P < 0.05$ was considered statistically significant.

Result

Patient characteristics

The sample selection procedure was illustrated in Fig. 1. The initial query yielded 7777 iPCN patients according to the inclusion criteria, including 6836 iIPMN patients, 504 iMCN patients, 418 iSPN patients, and 19 iSCN patients. In addition, 154,336 PDAC patients were enrolled in this study. The baseline characteristics of patients with iPCN are shown in Table 1. The median patient age at diagnosis was 69 (interquartile range (IQR), 61–77), 68 (IQR, 55–79), 35 (IQR, 24–47), and 71 (IQR, 62–75) years;

thus, it can be seen that iSPN mainly occurs in younger women. Among iIPMN patients, the primary lesions were mainly distributed in the pancreatic head, whereas for iMCN and iSPN patients, the lesions were mostly located in the body and tail of the pancreas. Significantly, iIPMN patients had a lower rate of radical surgery compared to other iPCN patients. In total, most neoplasms were advanced, with 10.8% at stage III and 63.1% at stage IV. More than 14 lymph nodes were examined in 32.8% of surgical patients and 8–14 lymph nodes were examined in 26.1% of surgical patients; lymph node metastasis was observed in 34.6% of patients with known lymph node status. Furthermore, the baseline characteristics of surgical patients with iPCN and PDAC are shown in Table S1.

Comparison of survival among iIPMN, iMCN, iSPN, iSCN, and PDAC patients in the SEER database

With regard to OS and CSS, Kaplan–Meier survival analysis was performed in the five pathological groups for the entire population and surgery group (Fig. 2), which showed more favorable outcomes in patients with iSPN and worse outcomes in patients with PDAC. Importantly, pairwise comparison showed that any two of the five pathological groups had a statistically significant difference (except iMCN vs. iSCN, $p = 0.06$ for OS, and $p = 0.217$ for CSS; all other $p < 0.05$, Tables S2, S3, S4 and S5). The 3-year OS and CSS rates in patients who underwent surgery were as follows: 45.7% and 50.1% for iIPMN, 54.8% and 59.3% for iMCN, 97.8% and 98.2% for iSPN, 88.9% and 88.9% for iSCN, and 27.3% and 30.5% for PDAC. In addition, the median OS and CSS times were 6 and 7 months for PDAC patients, compared to a median OS and CSS time of 8 and 9 months for iIPMN patients, and 17 and 24 months for iMCN patients, respectively ($P < 0.001$). By contrast, in the surgery group, the median OS and CSS times were increased to 19 and 20 months for PDAC patients, 31 and 37 months for iIPMN patients, and 54 and 137 months for iMCN patients, respectively ($P < 0.001$).

Multivariate analyses using the Cox proportional hazards model were used to evaluate the impact of known prognostic factors on OS and CSS in the surgery group. Based on the RCS results, the variable of regional nodes examined was categorized in the nomograms (<8, 8–14, >14). Similarly, age was stratified as a categorical variable (<56, 56–75, >75 years). As shown in Table S6, the types of PDAC and iIPMN, older age at diagnosis, male sex, Black race, head of pancreas, poorly differentiated grade, and more advanced T, N, or M stage were associated with poor outcomes, while the types of iMCN, iSPN, and iSCN, receiving chemotherapy and radiotherapy, diagnosis and treatment in the last decade, and more

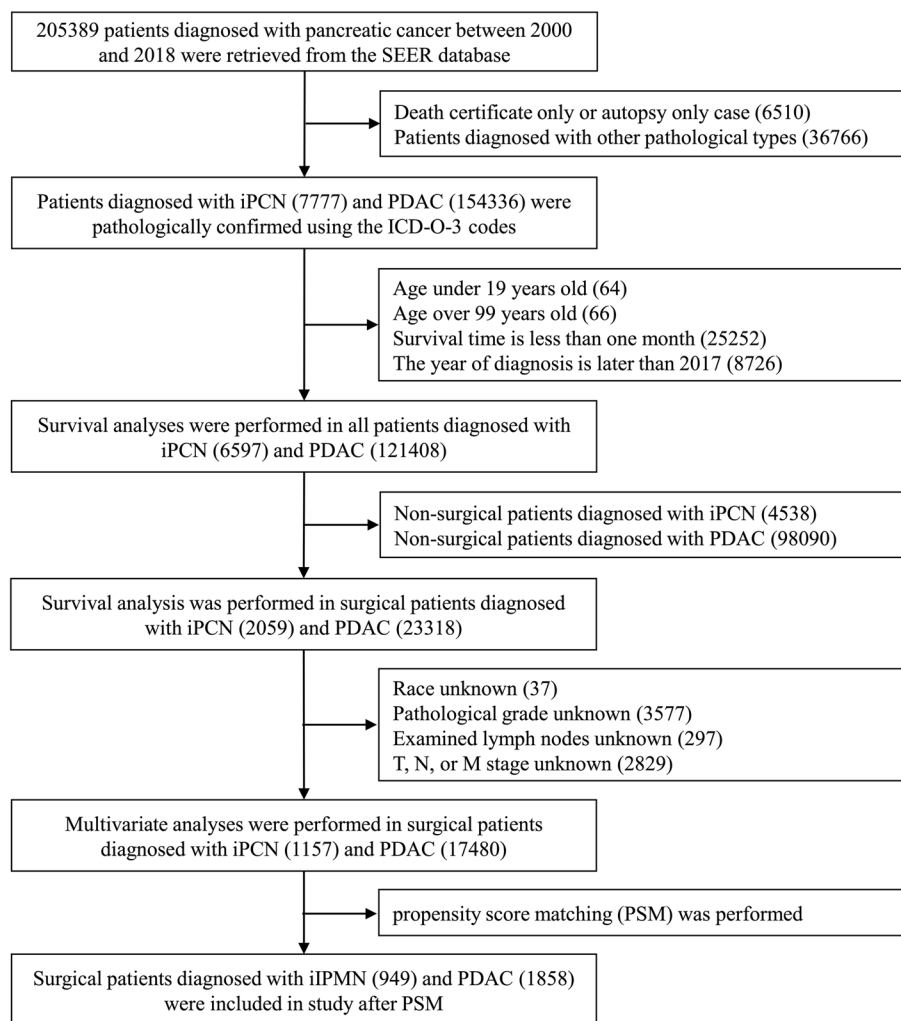


Fig. 1 Patient data selection process

regional nodes examined were associated with better outcomes.

To investigate the effect of adjuvant therapy on non-distant metastatic patients with different lymph node involvement statuses, multivariate analyses in subgroups of the N stage were performed. The results showed no clinical benefit from chemotherapy or radiotherapy in surgical patients with stage N0 or N1 iIPMN. The OS rate in stage N2 patients with iIPMN was improved by chemotherapy (HR, 1.785; 95% CI, 1.097–2.904; $P=0.020$ for OS), whereas no significant benefit from radiotherapy was observed in these patients. Owing to the insufficient number of iMCN patients, we only divided them into lymph node-negative and lymph node-positive groups and found that the clinical outcomes of the two groups did not improve with chemotherapy and radiotherapy.

We also explored the disparities in prognostic factors among mucinous types, and the results of multivariate

analyses indicated that age, pathologic grade, primary site, T stage, N stage, and regional nodes examined were the main independent risk factors for iIPMN, whereas for iMCN, only age, primary site, and N stage were independent risk factors. The results showed no statistically significant difference in the survival time of between Blacks and Whites among iIPMN and iMCN patients. Meanwhile, we found that patients with iIPMN located at the head of the pancreas were likely to have better prognosis (HR 1.314, $P=0.010$ for OS; and HR 1.274, $P=0.040$ for CSS); conversely, iMCN in the body and tail of pancreas had better prognosis (HR 0.542, $P=0.048$ for OS; and HR 0.453, $P=0.023$ for CSS).

To further demonstrate the better prognosis of postoperative patients with iIPMN over PDAC, we carried out a PSM between the two groups. Table S7 shows the baseline characteristics of the two groups before and after matching, and the differences in these variables were

Table 1 Demographic and clinicopathological characteristics of pancreatic cancer patients diagnosed with iIPMN, iMCN, iSPN, and iSCN

Variables	iIPMN (N=6836) (N, %)	iMCN (N=504) (N, %)	iSPN (N=418) (N, %)	iSCN (N=19) (N, %)	SUM (N=7777) (N, %)
Age					<0.001
<56	1007 (14.7)	137 (27.2)	364 (87.1)	2 (10.5)	1510 (19.4)
56–75	3793 (55.5)	194 (38.5)	49 (11.7)	13 (68.4)	4049 (52.1)
>75	2036 (29.8)	173 (34.3)	5 (1.2)	4 (21.1)	2218 (28.5)
Sex					<0.001
Female	3495 (51.1)	352 (69.8)	355 (84.9)	15 (78.9)	4217 (54.2)
Male	3341 (48.9)	152 (30.2)	63 (15.1)	4 (21.1)	3560 (45.8)
Race					<0.001
White	5562 (81.4)	395 (78.4)	284 (67.9)	15 (78.9)	6256 (80.4)
Black	745 (10.9)	61 (12.1)	78 (18.7)	2 (10.5)	886 (11.4)
Asian-Pacific	510 (7.5)	46 (9.1)	52 (12.4)	2 (10.5)	610 (7.8)
Unknown	19 (0.3)	2 (0.4)	4 (0.1)	0 (0)	29 (0.3)
Year of diagnosis					<0.001
2000–2008	3562 (52.1)	350 (69.4)	78 (18.7)	10 (52.6)	4000 (51.4)
2009–2018	3274 (47.9)	154 (30.6)	340 (81.3)	9 (47.4)	3777 (48.6)
Primary site					<0.001
Head	3002 (43.9)	131 (26.0)	115 (27.5)	6 (31.6)	3254 (41.8)
Body	790 (11.6)	65 (12.9)	70 (16.7)	1 (5.3)	926 (11.9)
Tail	1049 (15.3)	174 (34.5)	160 (38.3)	7 (36.8)	1390 (17.9)
others	1995 (29.2)	134 (26.6)	73 (17.5)	5 (26.3)	2207 (28.4)
Pathological grade					<0.001
I	686 (10.0)	69 (13.7)	66 (15.8)	4 (21.1)	825 (10.6)
II	1212 (17.7)	91 (18.1)	25 (6.0)	1 (5.3)	1329 (17.1)
III–IV	737 (10.8)	49 (9.7)	3 (0.7)	1 (5.3)	790 (10.2)
Unknown	4201 (61.5)	295 (58.5)	324 (77.5)	13 (68.4)	4833 (62.1)
Regional nodes examined					<0.001
0–7	5436 (79.5)	373 (74.0)	225 (53.8)	15 (78.9)	6049 (77.8)
8–14	443 (6.5)	60 (11.9)	100 (23.9)	1 (5.3)	604 (7.8)
>14	626 (9.2)	51 (10.1)	80 (19.1)	2 (10.5)	759 (9.8)
Unknown	331 (4.8)	20 (4.0)	13 (3.1)	1 (5.3)	365 (4.7)
T stage					<0.001
T1	504 (7.4)	48 (9.5)	43 (10.3)	0 (0.0)	595 (7.7)
T2	1418 (20.7)	67 (13.3)	113 (27.0)	1 (5.3)	1599 (20.6)
T3	1309 (19.1)	201 (40.0)	215 (51.4)	10 (52.6)	1735 (22.3)
T4	967 (14.1)	46 (9.1)	9 (2.2)	3 (15.8)	1025 (13.2)
Tx	3605 (52.7)	142 (28.2)	38 (9.1)	5 (26.3)	3790 (48.7)
N stage					<0.001
N0	1086 (15.9)	190 (37.7)	303 (72.5)	6 (31.6)	1585 (20.4)
N1	545 (8.0)	44 (8.7)	17 (4.1)	2 (10.5)	608 (7.8)
N2	213 (3.1)	15 (3.0)	1 (0.2)	0 (0.0)	229 (2.9)
Nx	4992 (73.0)	255 (50.6)	97 (23.2)	11 (57.9)	5355 (68.9)
M stage					<0.001
M0	2824 (41.3)	354 (70.2)	381 (91.1)	9 (47.4)	3568 (45.9)
M1	3689 (54.0)	106 (21.0)	27 (6.5)	9 (47.4)	3831 (49.3)
Mx	323 (4.7)	44 (8.7)	10 (2.4)	1 (5.3)	378 (4.9)
TNM stage					<0.001
IA	238 (3.5)	31 (6.2)	37 (8.9)	0 (0.0)	306 (3.9)

Table 1 (continued)

Variables	iIPMN (N=6836) (N, %)	iMCN (N=504) (N, %)	iSPN (N=418) (N, %)	iSCN (N=19) (N, %)	SUM (N=7777) (N, %)
IB	264 (3.7)	32 (6.3)	88 (21.1)	1 (5.3)	385 (5.0)
IIA	261 (3.8)	90 (17.9)	159 (38.0)	2 (10.5)	512 (6.6)
IIB	334 (4.9)	31 (6.2)	13 (3.1)	2 (10.5)	380 (4.9)
III	611 (8.9)	37 (7.3)	5 (1.2)	1 (5.3)	654 (8.4)
IV	3689 (54.0)	106 (21.0)	27 (6.5)	9 (47.4)	3831 (49.3)
Unknown	1439 (21.1)	177 (35.1)	89 (21.3)	4 (21.1)	1709 (22.0)
Surgery					<0.001
Yes	1653 (23.9)	283 (56.1)	366 (87.5)	10 (52.6)	2312 (29.7)
No/unknown	5183 (76.1)	221 (43.9)	52 (12.5)	9 (47.4)	5465 (70.3)
Radiotherapy					<0.001
Yes	1012 (14.8)	81 (16.1)	8 (1.9)	3 (15.8)	1104 (14.2)
No/unknown	5824 (85.2)	423 (83.9)	410 (98.1)	16 (84.2)	6673 (85.8)
Chemotherapy					<0.001
Yes	3337 (48.8)	155 (30.8)	25 (6.0)	6 (31.6)	3523 (45.3)
No/unknown	3499 (51.2)	349 (69.2)	393 (94.0)	13 (68.4)	4254 (54.7)

Abbreviations: iIPMN invasive intraductal papillary mucinous neoplasm, iMCN invasive mucinous cystic neoplasm, iSPN invasive solid pseudopapillary neoplasm, iSCN invasive serous cystic neoplasm

balanced. A Kaplan–Meier plot was performed in the tendentious matching queue (Fig. S1), which confirmed better prognosis in patients with iIPMN than in those with PDAC [median OS: 29 months vs 21 months (HR 0.747, $P < 0.001$); median CSS: 34 months vs 24 months (HR 0.707, $P < 0.001$)]. However, according to subgroup analysis, there was no statistically significant difference in CSS between postoperative patients with iIPMN and those with PDAC when the patient was Black, and the neoplasm was located in the body and tail of pancreas or staged as T4, N2, or M1 (Fig. 3).

Construction and validation of nomograms

To predict the survival time of patients with iPCN after surgical resection, new prediction models were established based on the Cox proportional hazards regression. Finally, the variables associated with OS and CSS were identified by backward stepwise selection as shown in Table 2. Nomograms to predict the 1-, 2-, and 3-year OS and CSS were created based on the selected variables. Figure 4 illustrates that histologic type contributed the most to survival, while chemotherapy or radiotherapy had the least effect, and lower total points of patients obtained by adding the points for each variable were associated with a more favorable prognosis.

The discriminative ability of the model was assessed using Kaplan–Meier curves stratified by the tertile of the total points of each patient calculated from the nomograms. As shown in Fig. S2, there were significant differences in the actual OS and CSS of patients

between different tertiles, and patients with the lowest points (tertile 1) had noticeably better outcomes (69.6% 3-year OS and 80.1% 3-year CSS) than patients in tertile 2 (26.6% 3-year OS and 53.5% 3-year CSS) and tertile 3 (8.9% 3-year OS and 17.3% 3-year CSS) ($P < 0.001$). In contrast, the approximate median 3-year OS of patients predicted by the model showed good estimates of 70%, 40%, and 15% in tertiles 1, 2, and 3, respectively ($P < 0.001$). Similarly, the median 3-year CSS rates were 75%, 52%, and 21% in tertiles 1, 2, and 3, respectively ($P < 0.001$).

To further evaluate the discriminative power of the newly established model, we compared the C-indexes and area under the curve (AUC) values with those of the 8th edition of the TNM staging system. The C-indexes for the new nomogram for the prediction of survival time were higher than those of the TNM staging system (0.725 vs. 0.666 OS and 0.736 vs. 0.683 CSS). The AUC values of the new nomograms that predicted 1-, 2-, and 3-year survival were 0.775, 0.786, and 0.800 (OS) and 0.775, 0.795, and 0.814 (CSS), respectively, whereas the AUC values of the TNM staging system were 0.693, 0.720, and 0.739 (OS) and 0.693, 0.730, and 0.748 (CSS), respectively (all $p < 0.001$) (Fig. 5). Additionally, the comparison of the ROC curve between the two models in the prediction of 5- and 10-year OS and CSS of surgical patients was shown in Fig. S3. The 350-sample bootstrapped calibration plots showed good agreement between the actual and predicted values for the 3-year OS and CSS (Fig. 6a, b). Finally, DCA

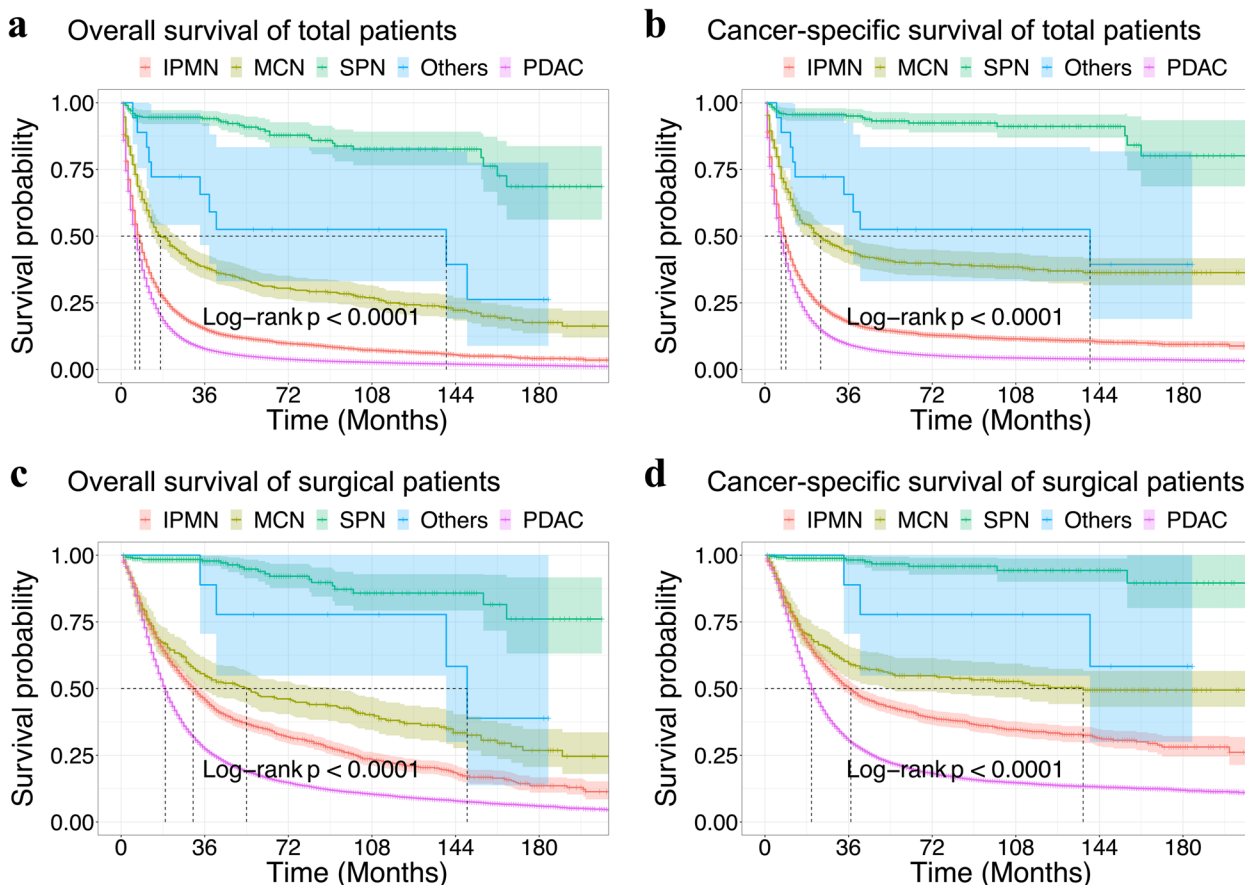


Fig. 2 Kaplan–Meier curves demonstrating overall survival (OS) and cancer-specific survival (CSS) in total patients (a, b) and patients who underwent radical surgery (c, d) according to histologic type

curves showed that the nomogram has greater clinical benefit in the prediction of 3-year OS and CSS (Fig. 6c, d).

Discussion

Recently, three important societies and study groups, the International Association of Pancreatology (IAP), the American Gastroenterological Association (AGA), and the European Study Group on Cystic Tumors of the Pancreas, proposed and updated their own guidelines for the diagnosis and management of PCN [6–8]. However, owing to the paucity of available studies, especially comprehensive ones, there has been a lack of consensus on accurate prognostication of outcomes and the optimal modality of surveillance for patients with iPCN in these guidelines. In this study, we identified nearly 8 thousand iPCN patients, including almost all pathological subtypes. We carried out a comprehensive analysis of all iPCN patient data in terms of demographic and clinicopathological characteristics and compared the differences in clinical outcomes between various subtypes.

Furthermore, nomograms were created to predict the survival rate of patients with iPCN who underwent curative resection and offered effective information to physicians and patients.

The OS rates for patients with PC have been reported to be very low worldwide [9], and the difference between PDAC and iPCN needs to be validated by large studies [10]. In our survival analysis of total patients, we found that the 3-year OS of iIPMN, iMCN, iSPN, iSCN, and PDAC was 15.2%, 38.2%, 94.0%, 65.7%, and 7.7%, respectively, implying that the prognosis of iPCN is much better than that of PDAC. Likewise, we analyzed patients undergoing radical surgery and found that the prognosis of all types of iPCN was improved and much better than that of PDAC, suggesting that complete surgical resection is also a key treatment modality for patients with iPCN. To further confirm the above findings, we performed multivariate analyses and demonstrated that the risk of death in PDAC increased by 39% compared to that in iIPMN. After adjusting for potential confounders using a propensity score-matched

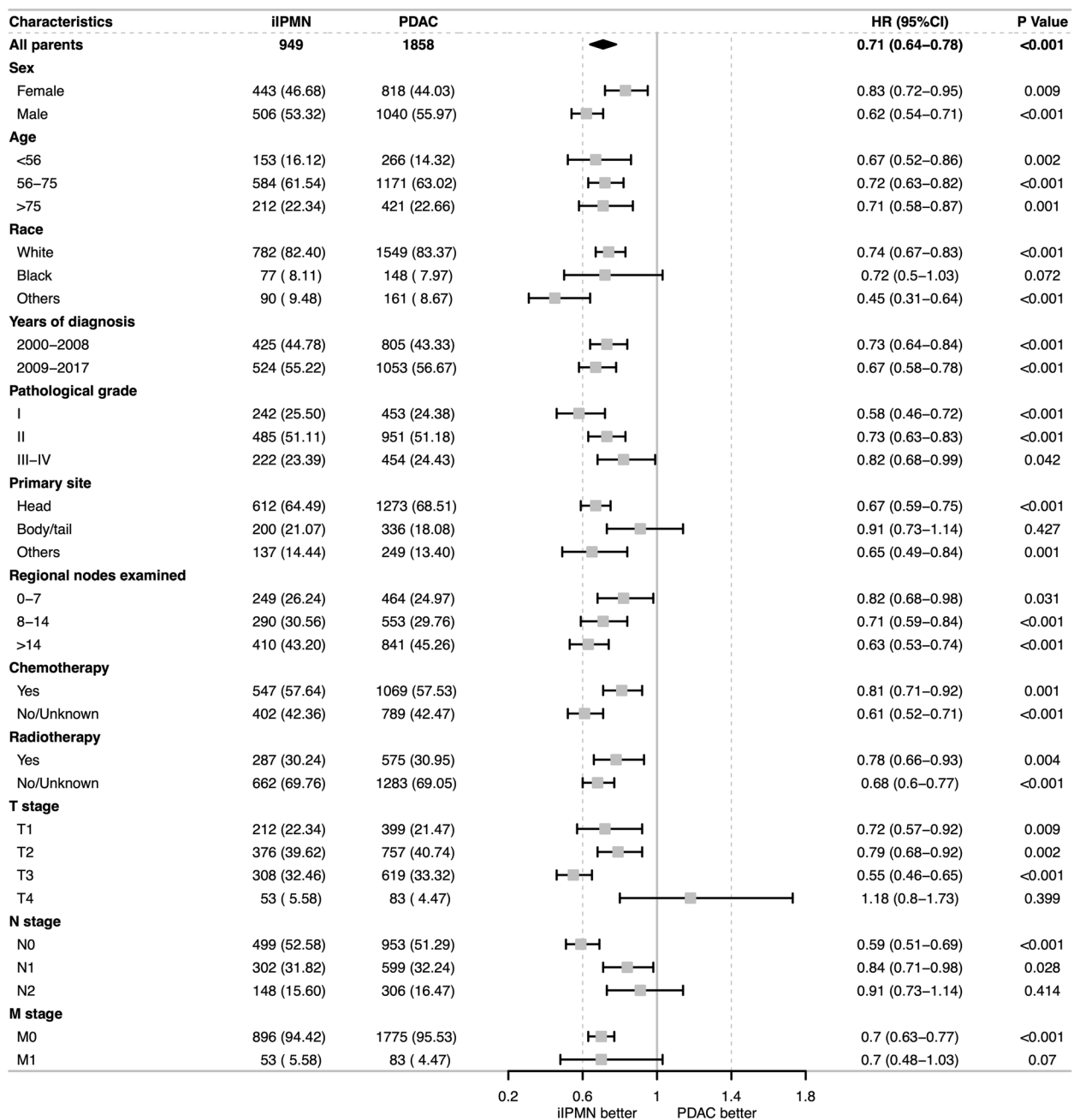


Fig. 3 Comparison of cancer-specific survival (CSS) among subgroups of iIPMN and PDAC patients who underwent curative resection after propensity score matching

analysis, the results showed that the clinical outcomes of iIPMN were still better than those of PDAC. However, subgroup analysis found that the survival differences were not significant in patients with advanced neoplasms (T4, N2, or M1), which is consistent with several recent studies [11, 12]. Hence, to improve clinical outcomes, long-term monitoring is crucial for the early detection of iIPMN.

Our results confirmed that chemotherapy reduced the risk of death in patients with stage N2 iIPMN, but it had no clinical benefit in lymph node-negative iPCN patients who underwent curative resection. Therefore, we recommend chemotherapy for iIPMN patients with lymph node positivity, which is consistent with previously published studies [13–16]. However, controversy exists on whether adjuvant treatment should be performed in

Table 2 Multivariate analysis of OS and CSS of iPCN patients who underwent curative resection using the Cox proportional hazards model

Variables	OS HR (95% CI)	P value	CSS HR (95% CI)	P value
Age				
< 56	1 [reference]		1 [reference]	
56–75	1.330 (1.069–1.653)	0.010	1.193 (0.945–1.506)	0.137
> 75	2.050 (1.599–2.627)	< 0.001	1.650 (1.259–2.163)	< 0.001
Sex				
Female	1 [reference]		1 [reference]	
Male	1.004 (0.860–1.173)	0.958	0.910 (0.767–1.080)	0.282
Race				
White	1 [reference]		1 [reference]	
Black	1.029 (0.788–1.345)	0.832	0.949 (0.699–1.290)	0.740
Others	0.639 (0.482–0.848)	0.002	0.653 (0.476–0.895)	0.008
Histologic type				
iIPMN	1 [reference]		1 [reference]	
iMCN	0.836 (0.649–1.077)	0.165	0.901 (0.682–1.191)	0.464
iSPN	0.034 (0.005–0.244)	< 0.001	NA	NA
iSCN	0.628 (0.086–4.562)	0.645	0.751 (0.103–5.479)	0.777
Pathological grade				
I	1 [reference]		1 [reference]	
II	1.521 (1.254–1.844)	< 0.001	1.563 (1.254–1.947)	< 0.001
III–IV	2.114 (1.684–2.653)	< 0.001	2.131 (1.655–2.743)	< 0.001
Year of diagnosis				
2000–2008	1 [reference]		1 [reference]	
2009–2017	0.827 (0.701–0.976)	< 0.025	0.785 (0.656–0.941)	0.009
Primary site				
Head	1 [reference]		1 [reference]	
Body and tail	1.105 (0.911–1.340)	0.312	1.045 (0.842–1.298)	0.690
Others	0.924 (0.684–1.247)	0.603	0.952 (0.685–1.323)	0.769
Chemotherapy				
Yes	1 [reference]		1 [reference]	
No/unknown	1.218 (1.011–1.469)	0.038	1.045 (0.851–1.283)	0.674
Radiotherapy				
Yes	1 [reference]		1 [reference]	
No/unknown	1.075 (0.889–1.301)	0.455	1.147 (0.934–1.408)	0.190
Regional nodes examined				
0–7	1 [reference]		1 [reference]	

Table 2 (continued)

Variables	OS HR (95% CI)	P value	CSS HR (95% CI)	P value
8–14	0.829 (0.686–1.003)	0.053	0.789 (0.639–0.973)	0.027
> 14	0.667 (0.548–0.813)	< 0.001	0.603 (0.484–0.751)	< 0.001
T stage				
T1	1 [reference]		1 [reference]	
T2	1.388 (1.103–1.747)	0.005	1.458 (1.125–1.890)	0.004
T3	1.309 (1.037–1.651)	0.023	1.266 (0.970–1.653)	0.083
T4	3.176 (2.219–4.547)	< 0.001	3.166 (2.139–4.688)	< 0.001
N stage				
N0	1 [reference]		1 [reference]	
N1	2.081 (1.733–2.500)	< 0.001	2.303 (1.881–2.821)	< 0.001
N2	2.822 (2.240–3.554)	< 0.001	3.212 (2.500–4.129)	< 0.001
M stage				
M0	1 [reference]		1 [reference]	
M1	1.624 (1.194–2.208)	0.002	1.749 (1.263–2.422)	< 0.001

Abbreviations: OS overall survival, CSS cancer-specific survival, iPCN invasive pancreatic cystic neoplasm, HR hazard ratio, iIPMN invasive intraductal papillary mucinous neoplasm, iMCN invasive mucinous cystic neoplasm, iSPN invasive solid pseudopapillary neoplasm, iSCN invasive serous cystic neoplasm

patients without lymph node involvement [17]. The 2018 European guidelines on PCN treatment recommended adjuvant systemic chemotherapy for iIPMN with or without positive lymph node status [8]. Based on our data, adjuvant chemotherapy should not be recommended as conventional therapy for patients with N0 stage, except for concurrent multiple risk factors, such as involvement of the celiac artery, superior mesenteric artery, and common hepatic artery; insufficient lymph nodes detection, and poor differentiation.

There is insufficient data to support radiotherapy for PCN-associated invasive carcinomas. A few studies showed that adjuvant radiotherapy alone or in combination with chemotherapy may be beneficial to node-positive iIPMN patients [14, 18], while no evidence is available to demonstrate the effect of radiotherapy on iMCN patients. Our study confirmed that there was no clinical benefit of radiotherapy in surgical iPCN patients with or without lymph node involvement. Moreover, we found no difference in survival time in iIPMN patients who received chemotherapy combined with radiotherapy or chemotherapy alone, regardless of lymph node involvement status.

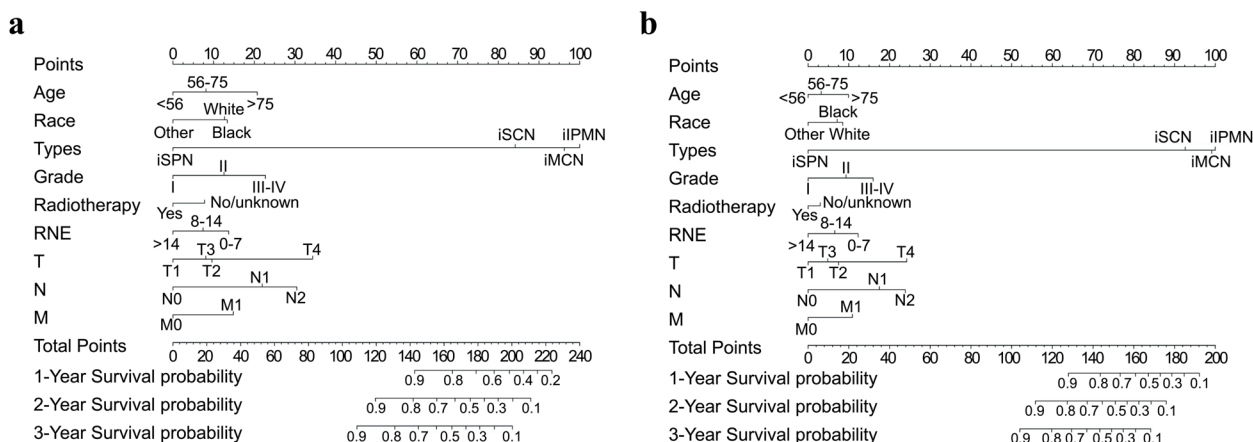


Fig. 4 The nomograms to predict overall survival (OS) (a) and cancer-specific survival (CSS) (b) were performed based on multivariate analyses using the Cox proportional hazard model. Abbreviations: RNE, regional nodes examined

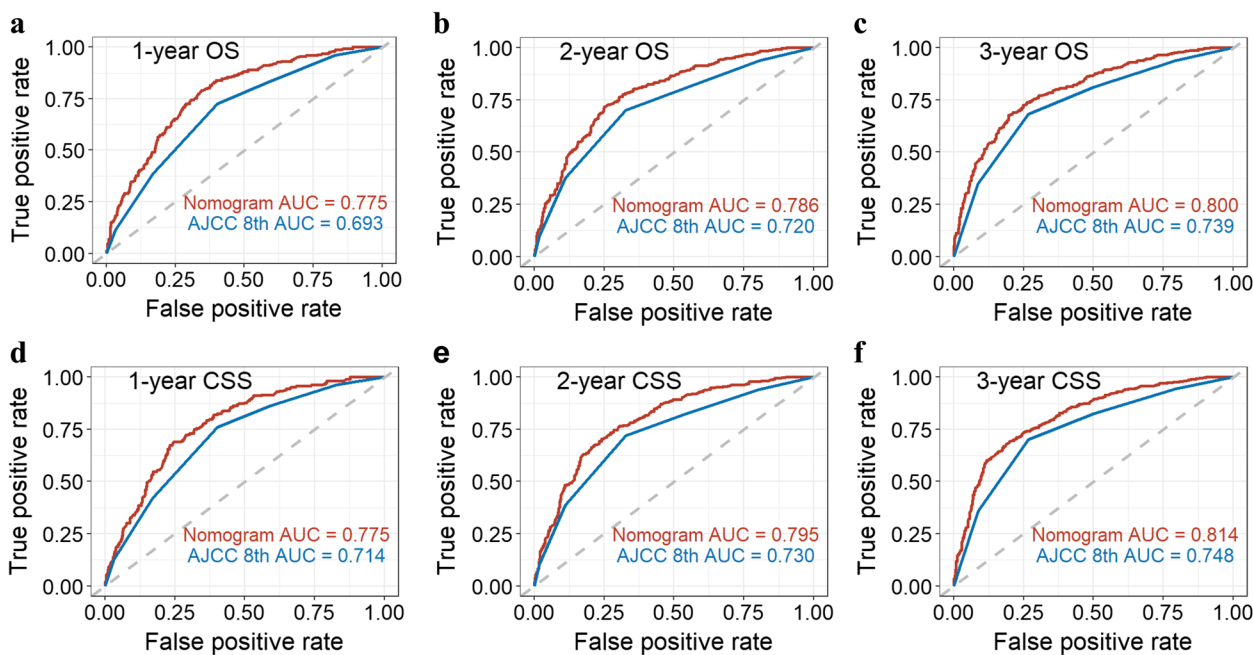


Fig. 5 Comparison of ROC curve between the nomogram and the AJCC 8th TNM staging system in prediction of clinical outcomes of iPCN patients who underwent curative resection at 1-, 2-, and 3-year points. **a** One-year OS predicting, **b** 2-year OS predicting, **c** 3-year OS predicting, **d** 1-year CSS predicting, **e** 2-year CSS predicting, and **f** 3-year CSS predicting

In general, the AJCC staging system used for staging PC has a good value for prognostic stratification of the total population; however, the estimation of clinical outcomes for each individual is impractical. Recently, as a more individualized prediction method, nomograms have been shown to provide prognostic information and guide accurate decision-making for treatment [19–21]. Currently, no good predictive model is available for prognostication of patients with PCN [22]. In this study, we created a nomogram to predict the outcomes of surgical

patients with iPCN based on the risk factors. Our model showed good discrimination, with an AUC value of 0.800 for predicting 3-year OS and 0.814 for 3-year CSS. We also performed a Kaplan–Meier analysis of the OS and CSS between the high-risk, medium-risk, and low-risk patients, stratified by the total points of each individual calculated by the predictive model. The results showed significant differences among groups, which graphically proved the good discriminative ability. Furthermore, the median predicted 3-year survival probability and the

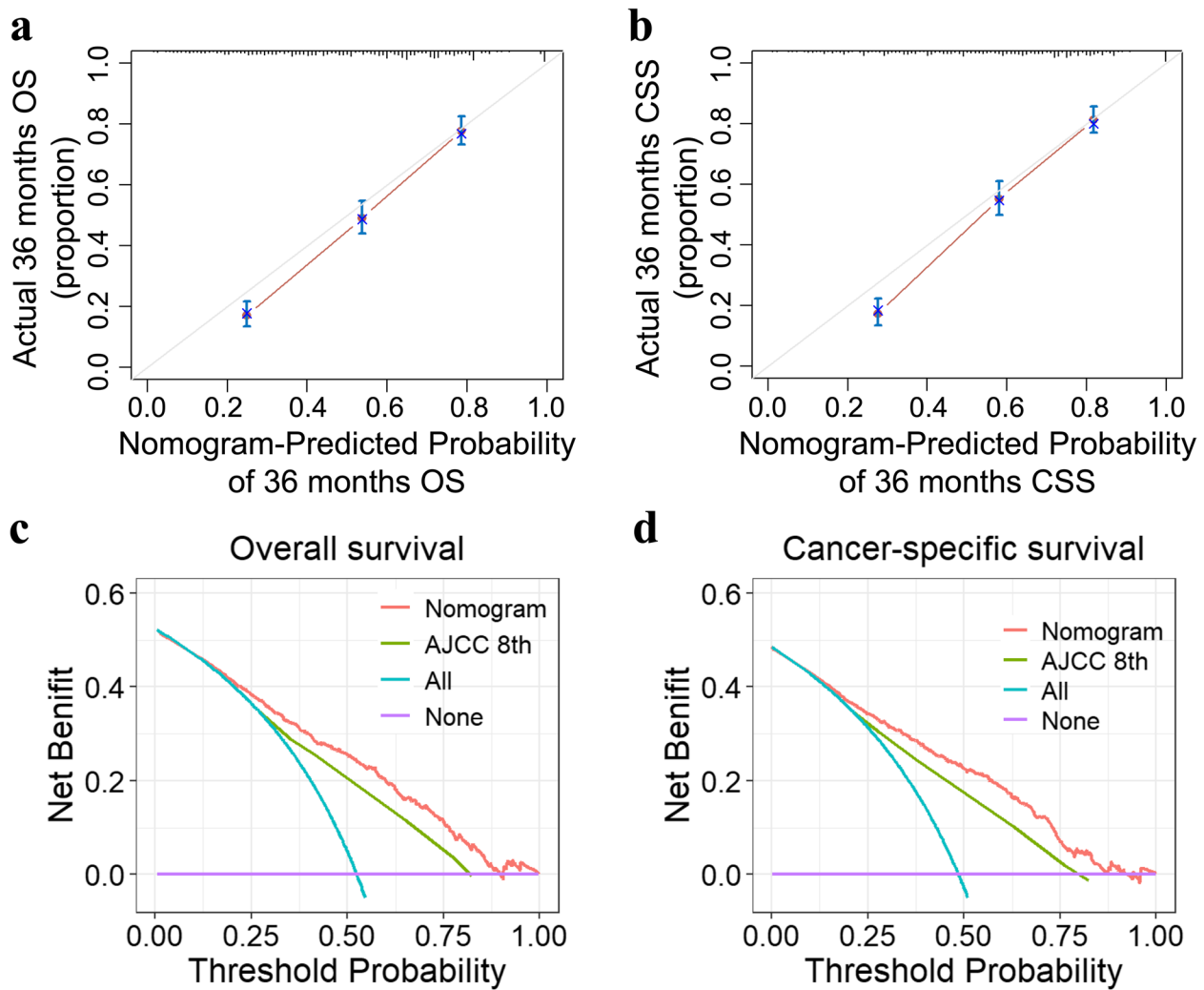


Fig. 6 Calibration plot of the nomogram for predicting 3-year overall survival (OS) (a) and cancer-specific survival (CSS) (b) rates and decision curve analysis (DCA) for the nomogram and the AJCC 8th staging system in prediction of 3-year OS (c) and CSS (d) rates

actual 3-year survival probability of each group were similar, which reflected good calibration ability. We also constructed a calibration plot for the prediction of 3-year OS and CSS. The predictions nearly fell along the 45-degree diagonal line, implying that the nomogram was a well-calibrated model. Also, we compared the predictive performance of the new model with the AJCC 8th staging system, and the results of the AUC and DCA showed that the new model has an absolute advantage in terms of discrimination and calibration. Collectively, these data strongly suggest that our proposed predictive model can provide information on the prognosis of iPCN patients undergoing curative resection.

The present study had several limitations. Firstly, some variables are not available in the SEER database, including laboratory test information such as serum CA19-9,

which is considered as one of the most effective PC markers, comorbidity information, radiographic findings, and details of intervention, such as the status of the surgical margin and the regimens, sequences, and courses of adjuvant treatment, all of which are important prognostic factors of iPCN based on past experience; hence, the potential effect of these variables in the predictive models could not be evaluated. Secondly, although we collected approximately 20 years' data on iPCN patients from 18 states across the USA, cases of special types of iPCN were still insufficient due to the extremely low incidence of these cystic cancers. Simultaneously cNET was not listed separately in the SEER database and could not be counted; therefore, partial analysis was limited. Finally, although the proposed nomograms showed better performance by internal validation than the AJCC staging

system, more studies using other databases are needed to externally validate our predictive models.

Conclusions

In conclusion, this large retrospective SEER-based population study showed that the prognosis of patients with iPCN subtypes was significantly better than that of PDAC patients. Several independently prognostic factors were identified to predict the OS and CSS of patients with iPCN who underwent curative resection. Based on these variables, a new survival prediction model was created and presented using nomograms, which demonstrated substantially better discrimination and calibration compared to the 8th AJCC staging system. Future studies are required for optimization of the nomograms through the addition of other important variables, such as laboratory tests, comorbidities, and treatment modalities, and further validation of their predictive value in other databases.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12957-023-03145-z>.

Additional file 1: Figure S1. Kaplan-Meier curves demonstrating overall survival (OS) (a) and cancer-specific survival (CSS) (b) in iIPMN and PDAC patients who underwent curative resection after propensity score matching.

Additional file 2: Figure S2. Kaplan-Meier Curves demonstrating overall survival (OS) (a) and cancer-specific survival (CSS) (b) in iPCN patients who underwent curative resection according to tertiles of predicted survival using the nomogram.

Additional file 3: Figure S3. Comparison of ROC curve between the nomogram and the AJCC 8th TNM staging system in prediction of clinical outcomes of iPCN patients who underwent curative resection at 5- and 10-year point. A: 5-year OS predicting, B: 5-year CSS predicting, C: 10-year OS predicting, D: 10-year CSS predicting.

Additional file 4: Table S1. Demographic and clinicopathological characteristics of surgical patients diagnosed with iIPMN, iMCN, iSPN, iSCN, and PDAC.

Additional file 5: Table S2. Pairwise comparisons using log-rank test to assess the overall survival difference between five pathological groups in the entire population.

Additional file 6: Table S3. Pairwise comparisons using log-rank test to assess the cancer-specific survival difference between five pathological groups in the entire population.

Additional file 7: Table S4. Pairwise comparisons using log-rank test to assess the overall survival difference between five pathological groups in the surgery patients.

Additional file 8: Table S5. Pairwise comparisons using log-rank test to assess the cancer-specific survival difference between five pathological groups in the surgery patients.

Additional file 9: Table S6. Multivariate analysis of OS and CSS of surgical patients diagnosed with iPCN and PDAC using the Cox proportional hazards model.

Additional file 10: Table S7. Demographic and clinicopathological characteristics of patients diagnosed with iIPMN and PDAC before and after propensity score matching.

Authors' contributions

Manuscript preparation: YS; study design: JS and YS; data collection: ZL; data analysis and interpretation: JX and HC. All authors confirmed that they contributed to the manuscript review by revising it critically for important intellectual content and have read and approved the final draft for submission. All authors are also responsible for the manuscript's content.

Funding

This research received no external funding.

Availability of data and materials

The SEER database is an open-access resource, and the study website <https://seer.cancer.gov/> has information on available data and access procedures. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 24 February 2023 Accepted: 13 August 2023

Published online: 23 August 2023

References

- Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76(2):182–8.
- Van Huijgevoort NCM, Del Chiaro M, Wolfgang CL, et al. Diagnosis and management of pancreatic cystic neoplasms: current evidence and guidelines. *Nat Rev Gastroenterol Hepatol*. 2019;16(11):676–89. <https://doi.org/10.1038/s41575-019-0195-x>.
- Kromrey ML, Bulow R, Hubner J, Paperlein C, Lerch MM, Ittermann T, et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut*. 2018;67(1):138–45.
- Del Chiaro M, Verbeke C, Salvia R, Kloppel G, Werner J, McKay C, et al. European experts consensus statement on cystic tumours of the pancreas. *Dig Liver Dis*. 2013;45(9):703–11.
- Jais B, Rebours V, Malleo G, Salvia R, Fontana M, Maggino L, et al. Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas). *Gut*. 2016;65(2):305–12.
- Tanaka M, Fernandez-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17(5):738–53.
- Vege SS, Ziring B, Jain R, Moayyedi P. Clinical Guidelines C, American Gastroenterology A. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology*. 2015;148(4):819–22; quiz 12–3.
- European Study Group on Cystic Tumours of the P. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut*. 2018;67(5):789–804.
- Wood LD, Canto MI, Jaffee EM, et al. Pancreatic cancer: pathogenesis, screening, diagnosis, and treatment. *Gastroenterology*. 2022;163(2):386–402.e381. <https://doi.org/10.1053/j.gastro.2022.03.056>.
- Kim HS, Han Y, Kang JS, et al. Fate of patients with intraductal papillary mucinous neoplasms of pancreas after resection according to the pathology and margin status: continuously increasing risk of recurrence even

- after curative resection suggesting necessity of lifetime surveillance. *Ann Surg.* 2022;276(4):e231–8. <https://doi.org/10.1097/sla.0000000000004478>.
11. Ziogas I A, Rodriguez Franco S, Schmoke N, et al. Comparison of invasive pancreatic ductal adenocarcinoma versus intraductal papillary mucinous neoplasm: a national cancer database analysis. *Cancers (Basel).* 2023; 15(4). <https://doi.org/10.3390/cancers15041185>.
 12. Holmberg M, Radkiewicz C, Strömberg C, et al. Outcome after surgery for invasive intraductal papillary mucinous neoplasia compared to conventional pancreatic ductal adenocarcinoma - a Swedish nationwide register-based study [J]. *Pancreatology.* 2023;23(1):90–7. <https://doi.org/10.1016/j.pan.2022.12.003>.
 13. McMillan MT, Lewis RS, Drebin JA, Teitelbaum UR, Lee MK, Roses RE, et al. The efficacy of adjuvant therapy for pancreatic invasive intraductal papillary mucinous neoplasm (IPMN). *Cancer.* 2016;122(4):521–33.
 14. Aronsson L, Marinko S, Ansari D, Andersson R. Adjuvant therapy in invasive intraductal papillary mucinous neoplasm (IPMN) of the pancreas: a systematic review. *Ann Transl Med.* 2019;7(22):689.
 15. Chong E, Ratnayake B, Dasari BVM, Loveday BPT, Siriwardena AK, Pandanaboyana S. Adjuvant chemotherapy in the treatment of intraductal papillary mucinous neoplasms of the pancreas: systematic review and meta-analysis. *World J Surg.* 2022;46(1):223–34.
 16. Liang H, Xie W, Lin X, et al. Pathologic T1 and T2 encapsulated invasive carcinomas arising from mucinous cystic neoplasms of the pancreas have favorable prognosis and might be treated conservatively. *J Pathol Clin Res.* 2021;7(5):507–16. <https://doi.org/10.1002/cjp2.225>.
 17. Choi M, Wang S E, Park J S, et al. Impact of adjuvant therapy in patients with invasive intraductal papillary mucinous neoplasms of the pancreas: an international multicenter cohort study. *Int J Surg.* 2023. <https://doi.org/10.1097/js9.0000000000000537>.
 18. Mungo B, Croce C, Oba A, Ahrendt S, Gleisner A, Friedman C, et al. Controversial role of adjuvant therapy in node-negative invasive intraductal papillary mucinous neoplasm. *Ann Surg Oncol.* 2021;28(3):1533–42.
 19. Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. *Lancet Oncol.* 2015;16(4):e173–180. [https://doi.org/10.1016/s1470-2045\(14\)71116-7](https://doi.org/10.1016/s1470-2045(14)71116-7).
 20. Crombé A, Spalato-Ceruso M, Michot A, et al. Gene expression profiling improves prognostication by nomogram in patients with soft-tissue sarcomas. *Cancer Commun (Lond).* 2022;42(6):563–6. <https://doi.org/10.1002/cac2.12268>.
 21. Wu J, Zhang H, Li L, et al. A nomogram for predicting overall survival in patients with low-grade endometrial stromal sarcoma: a population-based analysis. *Cancer Commun (Lond).* 2020;40(7):301–12. <https://doi.org/10.1002/cac2.12067>.
 22. Margonis GA, Pulvirenti A, Morales-Oyarvide V, et al. Performance of the 7th and 8th editions of the American Joint Committee on cancer staging system in patients with intraductal papillary mucinous neoplasm-associated PDAC: a multi-institutional analysis. *Ann Surg.* 2023;277(4):681–8. <https://doi.org/10.1097/sla.00000000000005313>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

