Original Article

The clinical characteristics of pancreatic colloid carcinoma and the development and validation of its cancer-specific survival prediction nomogram

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Background: Pancreatic colloid carcinoma (CC) is a subtype of pancreatic ductal adenocarcinoma (DAC) with low incidence but high malignancy. Unfortunately, there is no consensus regarding the clinical features and prognostic factors associated with CC, and the prognosis is unpredictable. We aimed to assess the clinicopathological characteristics of this rare disease and develop a nomogram for predicting cancer-specific survival (CSS) in CC.

Methods: We gathered comprehensive clinicopathological data from the Surveillance, Epidemiology, and End Results (SEER) database on 17,617 patients with DAC and 561 individuals with CC. Kaplan-Meier was used to plot each survival curve. Subsequently, we split the 561 patients with CC in a 7:3 split ratio between an internal training cohort (n=393) and an external validation cohort (n=168). The independent prognostic factors for CC patients in the training cohort were discovered using univariate and multivariate Cox regression analyses, and a nomogram was created. We assessed the nomogram's performance by using the concordance index (C-index), the area under the receiver operating characteristic curve (AUC), calibration curves, and decision curve analysis (DCA).

Results: The median for follow-up of CC patients was 15 months (range: 1–163 months), and the 1-, 3-, and 5-year CSS were 58.4%, 30.2% and 22.6%. For CC patients in the training cohort, age [hazard ratio (HR) =1.29; 95% confidence interval (CI): 1.00–1.65], sex (HR =0.64; 95% CI: 0.51–0.81), T3 stage (HR =2.21; 95% CI: 1.26–3.88), T4 stage (HR =2.76; 95% CI: 1.47–5.18), N1 stage (HR =1.29; 95% CI: 1.02–1.63), M1 stage (HR =1.60; 95% CI: 1.17–2.18), surgery (HR =0.30; 95% CI: 0.22–0.42), and radiotherapy (HR =0.76; 95% CI: 0.58–1.01) were the main predictors of the nomogram. The C-indexes of the training cohort and the validation cohort were 0.734 and 0.732, respectively. The 1-, 3-, and 5-year AUC values of the nomogram were predicted to be 0.827, 0.816, and 0.831 in the training cohort, 0.801, 0.841, and 0.835 in the validation cohort, respectively.

Conclusions: Based on several clinical features, we established the first predictive model of CC. This nomogram could be used to guide treatment decisions in patients with CC.

Keywords: Pancreatic ductal adenocarcinoma (pancreatic DAC); nomogram; survival analysis; calibration curve; pancreatic colloid carcinoma (pancreatic CC)

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Introduction

As per the World Health Organization (WHO) categorization of pancreatic ductal adenocarcinoma (DAC), pancreatic colloid carcinoma (CC), also termed mucinous non-cystic adenocarcinoma, is a histologic variation of DAC (1,2). Tubular, conventional, ordinary, or 'not-otherwise-specified' carcinoma is the most prevalent histological type of DAC. Pancreatic CC is an uncommon subtype of invasive pancreatic adenocarcinoma, responsible for only 1–3% of cases (3,4). On average, only a few cases of CC are believed to occur in 1 million people each year (3,5).

A separate subtype of DAC, known as pancreatic CC, differs histologically and clinically from common DAC. Histologically, CC is featured by clusters of neoplastic cells that make up at least 50% of the tumor and float in extracellular stromal mucin lakes. Clinically, CC patients exhibit a range of symptoms, including diarrhea, weight loss, and abdominal pain (6). CC can also be complicated by acute pancreatitis (7). These clinical manifestations are not significantly different from those of pancreatic DAC. Indeed, many cases of pancreatic CC have been misdiagnosed by pathologists as mucinous cystic tumors or signet-ring cell adenocarcinoma or classified as conventional DAC (8). It has been reported that CC demonstrates an indolent clinical behavior, with a slower rate of proliferation and a more favorable prognosis than DAC (9). The five-year survival rate is 55% for CC and 10% for ordinary DAC (6,10). As a result, pancreatic CC is thought to be a distinct kind of pancreatic cancer that needs to be distinguished from other pancreatic tumors.

Currently, there were few case reports of pancreatic CC, and the studies were limited by the small sample size of CC. The clinical manifestations of CC and DAC are extremely similar, making differentiation between them complicated (5). As an uncommon tumor, CC has a better prognosis than DAC; however, there is no clear consensus regarding its clinical characteristics and prognostic variables. Moreover, there were no studies on developing clinical prognostic models for CC. In the present study, we collected information on 18,178 patients from the Surveillance, Epidemiology, and End Results (SEER) database to investigate the variation in clinical features and survival outcomes between CC and DAC. We divided patients with CC into a training cohort and a validation cohort and developed a nomogram using clinicopathologic variables based on the training cohort. The nomogram seeks to forecast cancer-specific survival (CSS) probability values for CC cases over the course of 1, 3, and 5 years. We hope the nomogram shown here will be useful for optimizing follow-up protocols and enhancing long-term survival. We present the following article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-753/rc).

Highlight box

Key findings

- Our findings demonstrate that, in contrast to pancreatic ductal adenocarcinoma (DAC), pancreatic colloid carcinoma (CC) has better survival. A prognostic scoring model for the survival rate of CC patients was developed.

What is known, and what is new?

- CC is a rare subtype of pancreatic carcinoma with different clinical characteristics from pancreatic DAC.
- However, there is no clear consensus on the clinical characteristics and prognostic variables associated with CC, and the prognosis is unpredictable. This study established a new prognostic nomogram for CC patients to forecast the 1-, 3-, and 5-year cancer-specific survival (CSS).

What is the implication, and what should change now?

- Age, TNM stages, type of surgery, and radiotherapy should be considered when determining the prognosis of CC patients; a nomogram should be adopted to predict the survival rate of CC patients.

Methods

Study population and data sources

For this retrospective cohort study, the SEER registry was used. The National Cancer Institute in the United States funds the SEER database, a population-based database that compiles data on cancer incidence and survival rates. We looked at information on cases with CC and DAC from 2000 to 2018. Cancer data were periodically collected during the follow-up by identifying patients at the medical

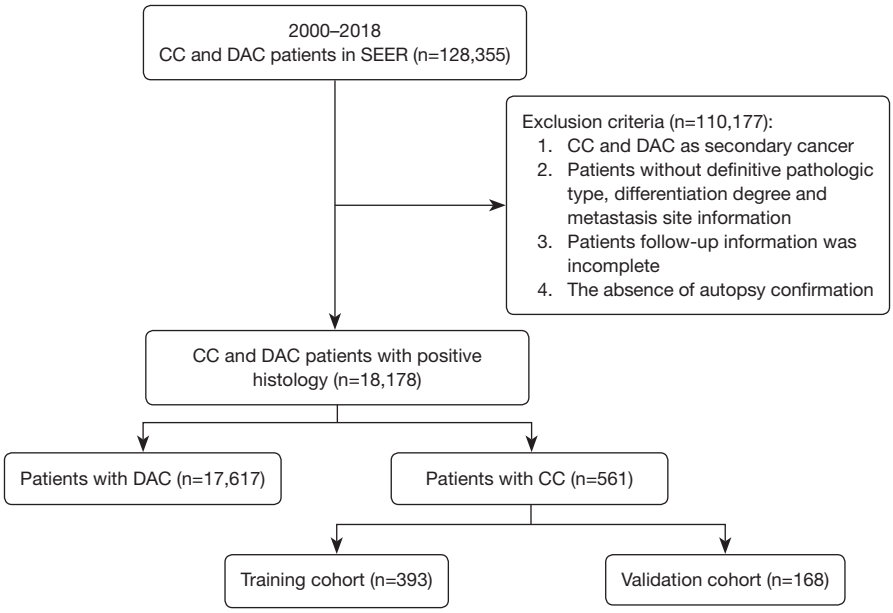

Figure 1 Flowchart for the study's participant recruitment. CC, colloid carcinoma; DAC, ductal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results.

institution, and cancer registries retrieved information about cancer from the medical records. All patients were followed until they died or until their last follow-up in December 2021, any lost to follow-up cases was excluded from the study. Tumors with a histology code of 8480 were classified as CC, whereas those with 8140, 8141, 8142, 8143, 8144, 8145, 8146, and 8147 codes were classified as DAC per the International Classification of Disease in Oncology (ICD-0-3). Positive exfoliative cytology with no positive histology and positive histology on pathological analysis both supported the diagnosis. For each patient, complete data was gathered on their age, gender, race, surgery, lymph node dissection, chemotherapy, marital status, radiotherapy, TNM stages, grade, tumor size, and tumor site. Cases without the aforementioned information were deleted. The exclusion criteria were as follows: (I) CC and DAC as secondary cancer; (II) the absence of information on the definitive pathologic type, differentiation degree, or metastasis site; (III) incomplete follow-up information; (IV) the absence of autopsy confirmation. The case selection flow diagram is presented in *Figure 1*. To increase the credibility and applicability of our study, we included as many patient records as possible from the database that met the aforementioned criteria. All data are publicly available, deidentified, and not subjected to Institutional Review Board approval. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Outcome measurement

We used CSS as the primary endpoint. As the cause of death, CC was used to define CSS, which was calculated from the time of diagnosis to cancer-associated death or the end of follow-up. Baseline parameters were evaluated to ascertain whether there were significant variations in the study population's distribution into CC and DAC groups. Investigators who were blind to the research predictor variables reviewed and noted all of the patients' demographic and clinical details, and the records of patient survival information were established without considering the subjective judgment of the investigators, instead relying on the death certificates.

Nomogram construction and validation

To produce a useful CSS nomogram of CC, we randomly split the SEER database into training and validation cohorts with a 7:3 split ratio. We also compared basic clinical information between the training and validation cohorts. In the training cohort, the independent prognostic factors included age, sex, TNM stages, surgery, and radiotherapy. These were found using a multivariate Cox proportional hazards regression analysis. The training cohort was then used to develop a nomogram based on these prognostic variables to forecast CSS for the first, third, and fifth years.

We evaluated the nomogram's anticipated accuracy and discrimination by using the concordance index (C-index), receiver operating characteristic curve (ROC), and area under the curve (AUC). The validation cohort's clinical data were then used for external validation, and calibration curves were created. The nomogram's discriminatory ability was considered acceptable when its C-indexes fall between 0.7 and 1.0. For calibration, the expected probability of the nomogram was contrasted with the actual possible outcomes. Utilizing 1,000 bootstrap resamples, the nomogram's predictive power was assessed. The nomogram's clinical utility was evaluated using a decision curve analysis (DCA).

Patient risk stratification

The total scores were computed from the nomogram based on the cut-off values computed by the X-tile software program (version 3.6.1). The training cohort was divided into low- and high-risk groups based on their scores. With the help of Kaplan-Meier survival analyses, we compared the two groups. The validation cohort verified the prediction model.

Statistical analysis

R software was used to conduct all statistical analyses (version 4.0.3). The Chi-square test was used to compare categorical variables between various groups. Kaplan-Meier survival curves were created to evaluate CSS, and the log-rank test was used to compare them. The prognostic factors of the patients in the training cohort were examined using univariate Cox proportional hazards regression, and the variables with statistical significance in the univariate analysis, as well as the prognostic factors in conjunction with clinical research, were then included in the multivariate Cox proportional hazards regression model to determine the final independent prognostic factors. Cox regression modeling was used to conduct a multivariate analysis of the training cohort, and a stepwise process was used to choose the covariates. Then, using R, we constructed the nomogram, calculated the C-index, and simultaneously drew ROC and calibration curves. The X-tile software program was used to quantify the cut-off value to ascertain the variations in CC patients' survival rates. A P value <0.05 was considered statistically significant for all two-sided statistical tests.

Results

Basic clinical information and survival analysis

From 2000 to 2018, a total of 561 people were diagnosed with CC, and 17,617 were diagnosed with DAC. *Table 1* demonstrates the features of these cases. We found that there were more elderly patients (≥65 years old) and those of White race in both the CC and DAC cohorts, while the sex distribution was relatively even. The median follow-up for the survivors was 15 months in the CC cohort and 11 months in the DAC cohort. Most cases with DAC and CC tended to have stage III cancer. Patients with DAC were more likely to present with N1 stage than those with CC (54% *vs.* 44.9%). Long-distance metastases were found in 137 patients with CC and 4,403 patients with DAC (24.4% *vs.* 25%). CC tumors were generally larger than 4 cm, while DAC tumors measured mostly 2–4 cm. Histopathologically, most patients with CC and DAC had Grade II stage tumors. Nevertheless, cases with CC tended to have more well-differentiated tumors than those with DAC (28% *vs.* 10.6%). In terms of tumor location, they were most commonly found in the pancreas head (58.8% in CC and 66.7% in DAC). Tumors located in the pancreas body had the lowest incidence in patients with CC and DAC (11.9% *vs.* 10.5%). Therapeutically, CC and DAC patients were more likely to undergo surgery (61.7% *vs.* 58.8%). Patients with CC and DAC both underwent lymph node dissections for at least four lymph nodes, with CC patients accounting for 54.2% and DAC patients for 53.9%. In addition, the majority of CC and DAC cases received postoperative chemotherapy (61.1% *vs.* 64.9%); however, most did not receive postoperative radiotherapy (72.2% *vs.* 70.9%). After that, we used the Kaplan-Meier technique to conduct a survival analysis of CC and DAC patients and discovered that CC patients had a longer survival time than DAC patients (*Figure 2*). The 1-, 3-, and 5-year CSS was 58.4%, 30.2%, and 22.6% in patients with CC versus 47.2%, 16.5%, and 10.5% in patients with DAC, respectively.

Univariate and multivariate analyses of CSS prognostic factors

The CC cases that were screened were split 7:3 into a training cohort (393 cases) and a validation cohort (168 cases). Age, gender, race, marital status, M stage, N stage, tumor size, tumor site, tumor differentiation, surgery, number of lymph node dissections, radiotherapy, and

Table 1 Demographic and clinical features of the DAC and CC cohorts

Characteristics	Adenocarcinoma (N=17,617)	Colloid (N=561)	Overall (N=18,178)	P
Age				0.06
<65 years	7,604 (43.2%)	219 (39.0%)	7,823 (43.0%)	
≥65 years	10,013 (56.8%)	342 (61.0%)	10,355 (57.0%)	
Sex				0.41
Female	8,651 (49.1%)	265 (47.2%)	8,916 (49.0%)	
Male	8,966 (50.9%)	296 (52.8%)	9,262 (51.0%)	
Race				0.05
American Indian/Alaska Native	86 (0.5%)	2 (0.4%)	88 (0.5%)	
Asian or Pacific Islander	1,335 (7.6%)	59 (10.5%)	1,394 (7.7%)	
Black	2,112 (12.0%)	57 (10.2%)	2,169 (11.9%)	
White	14,084 (79.9%)	443 (79.0%)	14,527 (79.9%)	
Marital status				0.99
Divorced	1,766 (10.0%)	57 (10.2%)	1,823 (10.0%)	
Married	10,685 (60.7%)	341 (60.8%)	11,026 (60.7%)	
Single	5,166 (29.3%)	163 (29.1%)	5,329 (29.3%)	
T stage				<0.01
T1	740 (4.2%)	40 (7.1%)	780 (4.3%)	
T2	3,163 (18.0%)	117 (20.9%)	3,280 (18.0%)	
T3	10,938 (62.1%)	314 (56.0%)	11,252 (61.9%)	
T4	2,776 (15.8%)	90 (16.0%)	2,866 (15.8%)	
M stage				0.80
M0	13,214 (75.0%)	424 (75.6%)	13,638 (75.0%)	
M1	4,403 (25.0%)	137 (24.4%)	4,540 (25.0%)	
N stage				<0.01
N0	8,108 (46.0%)	309 (55.1%)	8,417 (46.3%)	
N1	9,509 (54.0%)	252 (44.9%)	9,761 (53.7%)	
Tumor size				<0.01
<2 cm	2,102 (11.9%)	80 (14.3%)	2,182 (12.0%)	
2–4 cm	8,139 (46.2%)	195 (34.8%)	8,334 (45.8%)	
>4 cm	7,376 (41.9%)	286 (51.0%)	7,662 (42.1%)	
Tumor site				<0.01
Body	1,846 (10.5%)	67 (11.9%)	1,913 (10.5%)	
Head	11,752 (66.7%)	330 (58.8%)	12,082 (66.5%)	
Other	2,169 (12.3%)	84 (15.0%)	2,253 (12.4%)	
Tail	1,850 (10.5%)	80 (14.3%)	1,930 (10.6%)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Adenocarcinoma (N=17,617)	Colloid (N=561)	Overall (N=18,178)	P
Grade				<0.01
Grade I (well differentiated)	1,863 (10.6%)	157 (28.0%)	2,020 (11.1%)	
Grade II (moderately differentiated)	8,244 (46.8%)	253 (45.1%)	8,497 (46.7%)	
Grade III (poorly differentiated)	7,245 (41.1%)	144 (25.7%)	7,389 (40.6%)	
Grade IV (undifferentiated; anaplastic)	265 (1.5%)	7 (1.2%)	272 (1.5%)	
Surgery				0.18
No surgery	7,262 (41.2%)	215 (38.3%)	7,477 (41.1%)	
Surgery	10,355 (58.8%)	346 (61.7%)	10,701 (58.9%)	
Lymph node dissection				0.18
0	7,327 (41.6%)	223 (39.8%)	7,550 (41.5%)	
1–3	788 (4.5%)	34 (6.1%)	822 (4.5%)	
≥4	9,502 (53.9%)	304 (54.2%)	9,806 (53.9%)	
Chemotherapy				0.08
No	6,187 (35.1%)	218 (38.9%)	6,405 (35.2%)	
Yes	11,430 (64.9%)	343 (61.1%)	11,773 (64.8%)	
Radiotherapy				0.56
No	12,495 (70.9%)	405 (72.2%)	12,900 (71.0%)	
Yes	5,122 (29.1%)	156 (27.8%)	5,278 (29.0%)	
Survival time, months				<0.01
Mean (SD)	18.6 (23.4)	26.8 (31.6)	18.9 (23.7)	
Median (min, max)	11.0 (0, 167)	15.0 (0, 163)	11.0 (0, 167)	

DAC, ductal adenocarcinoma. CC, colloid carcinoma; SD, standard deviation.

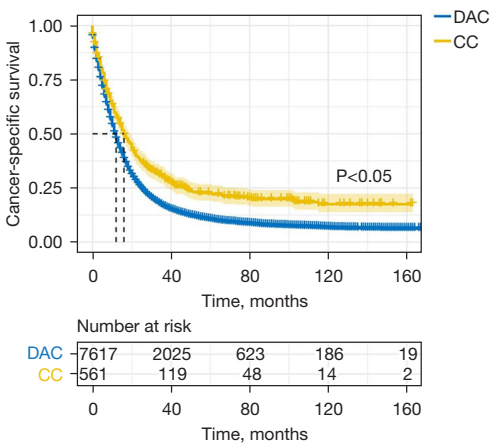

Figure 2 KM curves depicting the CSS of DAC and CC. DAC, ductal adenocarcinoma; CC, colloid carcinoma; KM curves, Kaplan-Meier curves; CSS, cancer-specific survival.

chemotherapy did not differ significantly between the two groups (*Table 2*). To identify the independent risk factors, we conducted univariate and multivariate Cox regression analyses, concentrating on the CSS of CC patients in the training cohort. The outcomes are shown in *Table 3*. In the univariate analysis, age, male, T and M stages, tumor size, poor differentiation, surgery, lymph node dissection, and radiotherapy were potentially associated with CSS. Clinically significant indices and variables with a P value <0.01 in the Cox univariate analysis were further analyzed using multivariate analysis. According to the multivariate analyses, age [≥65 *vs.* <65: hazard ratio (HR) =1.29; 95% confidence interval (CI): 1.00–1.65; P=0.04], sex (male *vs.* female: HR =0.64; 95% CI: 0.51–0.81; P<0.01), T3 stage (*vs.* T1 stage: HR =2.21; 95% CI: 1.26–3.88; P<0.01), T4 stage (*vs.* T1 stage: HR =2.76; 95% CI: 1.47–5.18; P<0.01),

N1 stage (*vs.* N0 stage: HR =1.29; 95% CI: 1.02–1.63; P=0.04), M1 stage (*vs.* M0 stage: HR =1.60; 95% CI: 1.17–2.18; P<0.01), surgery (*vs.* no surgery: HR =0.30; 95% CI: 0.22–0.42; P<0.01), and radiotherapy (*vs.* no radiotherapy: HR =0.76; 95% CI: 0.58–1.01; P=0.05) were independently correlated with the CSS of patients with CC.

Nomogram validation and construction

The nomogram's development was predicted on the above independent prognostic parameters in the training cohort, as demonstrated in *Figure 3*. Each factor is represented in the nomogram. The score for each CC patient was determined by multiplying the values of each factor, which ranged from 0 to 100 points. The nomogram calculated the 1-, 3-, and 5-year CSS based on the total points of the patients. A C-index value of 0.734 was found in the internal training cohort analysis for CSS nomogram predictions. The C-index for forecasting the CSS in the external validation cohort was 0.732. The 1-, 3-, and 5-year CSS AUC values for the training cohort were predicted to be 0.827, 0.816, and 0.831, respectively, and 0.801, 0.841, and 0.835 in the validation cohort, all of which were greater than 0.7 (*Figure 4*). In the calibration plots (*Figure 5*), the diagonal reference line indicates parity between the probability of survival as predicted by bootstraps and the actual survival rate. The DCA is shown in *Figure 6A*. These results show that the nomogram developed in this study was an effective prognostic predictor for calculating the long-term CSS for CC cases who have survived for 1, 3, and 5 years.

Risk stratification as per the nomogram

The overall score of the training group of CC patients was determined using the nomogram model. The range of the overall score was 0–350. The training cohort was split into low-risk (n=134) and high-risk (n=258) groups using the ideal cut-off value of 216. The validation cohort was divided into groups using the same cut-off values. *Figure 6B* depicts the survival curves after the log-rank test and the Kaplan-Meier CSS analysis. The survival rate of cases allocated to the low-risk group was significantly higher (P<0.05).

Discussion

The clinical signs of pancreatic CC are comparable to those of DAC and are typically mild, including jaundice, weight loss, abdominal pain, and an abdominal lump (5). The differential diagnosis of the two types is critical, as the biological and molecular distinctions between them lead to a more aggressive clinical course, a better surgical outcome, and a higher survival rate for CC. Currently, no large-sample studies exist on the 1-, 3-, or 5-year survival rates for CC. To our knowledge, our study is the most extensive analysis so far of CC. It is also the first to compare clinical baseline characteristics and survival differences between them and generate a nomogram to determine the prognosis of CC cases.

Our study has shown that managing CC and DAC can be made easier by identifying variations in patient demographics and tumor features. By studying their clinicopathological features, we found that CC and DAC, like other tumors, were more common in elderly patients (11). This could be because older patients frequently have more comorbid conditions. According to the WHO, males are more likely than females to suffer from pancreatic cancer, and this gender disparity seems much greater in developed countries. Our outcomes are consistent with those of prior studies (4,6,12). In our study, most CC and DAC tumors were in the more advanced T stages, which is typical of most malignancies. The later the T stage, the worse the prognosis. Metastasis (the spread and proliferation of cancer cells in an organ other than the one they originated from) is the induction of mortality in cancer cases. The current AJCC staging criteria follow the basic paradigm of tumor progression: as the tumor grows, tumor cells acquire more mutations and eventually gain the potential to spread to regional lymph nodes and distant organs (13,14). A previous study reported that the rate of distant metastasis in DAC patients was 30.6% (15). In our study, the distant metastasis rates in DAC and CC were 25% and 24.4%, respectively, and the lymph node metastatic rates of DAC and CC were 54% and 44.9%, respectively, which is attributable to CC tumors' relative indolence. According to a previous study, the tumor size of CC is larger than that of DAC (mean size: 5.3 *vs.* 3.5 cm) (6). The CC's diameter varied between 1.2 and 16.0 cm, which is higher than that of tubular DAC at presentation (3,16). In our study, the majority of CC tumors measured 4 cm in diameter, whereas the majority of DAC tumors measured 2–4 cm in diameter. In general, CC tumors were larger than DAC tumors. The CSS rate of pancreatic body or tail cancer has historically been lower than that of pancreatic head cancer owing to its distant or advanced metastatic state and lower R0 resection rate (17-19). Our analysis confirmed the previous findings.

Although the five-year survival rate for CC varies from

Table 2 Demographic and clinical features of the training and validation cohorts

Characteristics	Training cohort (N=393)	Validation cohort (N=168)	Overall (N=561)	P
Age				1.00
<65 years	153 (39.0%)	66 (39.1%)	219 (39.0%)	
≥65 years	239 (61.0%)	103 (60.9%)	342 (61.0%)	
Sex				1.00
Female	185 (47.2%)	80 (47.3%)	265 (47.2%)	
Male	207 (52.8%)	89 (52.7%)	296 (52.8%)	
Race				0.39
American Indian/Alaska Native	1 (0.3%)	1 (0.6%)	2 (0.4%)	
Asian or Pacific Islander	42 (10.7%)	17 (10.1%)	59 (10.5%)	
Black	45 (11.5%)	12 (7.1%)	57 (10.2%)	
White	304 (77.6%)	139 (82.2%)	443 (79.0%)	
Marital status				0.16
Divorced	39 (9.9%)	18 (10.7%)	57 (10.2%)	
Married	248 (63.3%)	93 (55.0%)	341 (60.8%)	
Single	105 (26.8%)	58 (34.3%)	163 (29.1%)	
T stage				0.04
T1	35 (8.9%)	5 (3.0%)	40 (7.1%)	
T2	84 (21.4%)	33 (19.5%)	117 (20.9%)	
T3	216 (55.1%)	98 (58.0%)	314 (56.0%)	
T4	57 (14.5%)	33 (19.5%)	90 (16.0%)	
M stage				0.26
M0	302 (77.0%)	122 (72.2%)	424 (75.6%)	
M1	90 (23.0%)	47 (27.8%)	137 (24.4%)	
N stage				0.66
N0	213 (54.3%)	96 (56.8%)	309 (55.1%)	
N1	179 (45.7%)	73 (43.2%)	252 (44.9%)	
Tumor size				0.22
<2 cm	62 (15.8%)	18 (10.7%)	80 (14.3%)	
2–4 cm	193 (49.2%)	93 (55.0%)	286 (51.0%)	
>4 cm	137 (34.9%)	58 (34.3%)	195 (34.8%)	
Tumor site				0.95
Body	45 (11.5%)	22 (13.0%)	67 (11.9%)	
Head	231 (58.9%)	99 (58.6%)	330 (58.8%)	
Other	60 (15.3%)	24 (14.2%)	84 (15.0%)	
Tail	56 (14.3%)	24 (14.2%)	80 (14.3%)	

Table 2 *(continued)*

Table 2 *(continued)*

Characteristics	Training cohort (N=393)	Validation cohort (N=168)	Overall (N=561)	P
Grade				0.78
Grade I (well differentiated)	113 (28.8%)	44 (26.0%)	157 (28.0%)	
Grade II (moderately differentiated)	177 (45.2%)	76 (45.0%)	253 (45.1%)	
Grade III (poorly differentiated)	98 (25.0%)	46 (27.2%)	144 (25.7%)	
Grade IV (undifferentiated; anaplastic)	4 (1.0%)	3 (1.8%)	7 (1.2%)	
Surgery				0.37
No surgery	145 (37.0%)	70 (41.4%)	215 (38.3%)	
Surgery	247 (63.0%)	99 (58.6%)	346 (61.7%)	
Lymph node dissection				0.59
0	151 (38.5%)	72 (42.6%)	223 (39.8%)	
1–3	23 (5.9%)	11 (6.5%)	34 (6.1%)	
≥4	218 (55.6%)	86 (50.9%)	304 (54.2%)	
Chemotherapy				0.24
No	159 (40.6%)	59 (34.9%)	218 (38.9%)	
Yes	233 (59.4%)	110 (65.1%)	343 (61.1%)	
Radiotherapy				0.76
No	281 (71.7%)	124 (73.4%)	405 (72.2%)	
Yes	111 (28.3%)	45 (26.6%)	156 (27.8%)	
Survival time, months				<0.01
Mean (SD)	28.0 (32.9)	23.8 (28.3)	26.8 (31.6)	
Median (min, max)	16.0 (0, 163)	15.0 (0, 153)	15.0 (0, 163)	

SD, standard deviation.

Table 3 Univariate and multivariate Cox regression analyses of CSS in CC cases (the training cohort)

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age						
<65	Reference			Reference		
≥65	1.26	0.99–1.60	0.06	1.29	1.00–1.65	0.04
Sex						
Female	Reference			Reference		
Male	0.71	0.57–0.89	<0.01	0.64	0.51–0.81	<0.01
T stage						
T1	Reference			Reference		
T2	2.71	1.51–4.86	<0.01	1.62	0.88–2.98	0.12

Table 3 *(continued)*

Table 3 *(continued)*

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
T3	2.29	1.33–3.96	<0.01	2.21	1.26–3.88	<0.01
T4	4.77	2.65–8.58	<0.01	2.76	1.47–5.18	<0.01
N stage						
N0	Reference			Reference		
N1	1.17	0.94–1.48	0.17	1.29	1.02–1.63	0.04
M stage						
M0	Reference			Reference		
M1	3.19	2.47–4.12	<0.01	1.60	1.17–2.18	<0.01
Tumor size						
<2 cm	Reference					
2–4 cm	1.46	1.01–2.12	0.04			
>4 cm	1.79	1.26–2.54	<0.01			
Tumor site						
Head	Reference					
Body	1.72	1.20–2.46	<0.01			
Tail	1.27	0.95–1.81	0.10			
Other	1.31	0.92–1.75	0.14			
Grade						
Grade I (well differentiated)	Reference					
Grade II (moderately differentiated)	1.1	0.83–1.46	0.51			
Grade III (poorly differentiated)	1.44	1.05–1.97	0.02			
Grade IV (undifferentiated; anaplastic)	1.35	0.49–3.68	0.56			
Surgery						
No surgery	Reference			Reference		
Surgery	0.24	0.19–0.30	<0.01	0.3	0.22–0.42	<0.01
Lymph node dissection						
0	Reference					
1–3	0.52	0.32–0.84	<0.01			
≥4	0.28	0.22–0.35	<0.01			
Radiotherapy						
No	Reference			Reference		
Yes	0.449	0.34–0.59	<0.01	0.76	0.58–1.01	0.05

CSS, cancer-specific survival; CC, colloid carcinoma; HR, hazard ratio; CI, confidence interval.

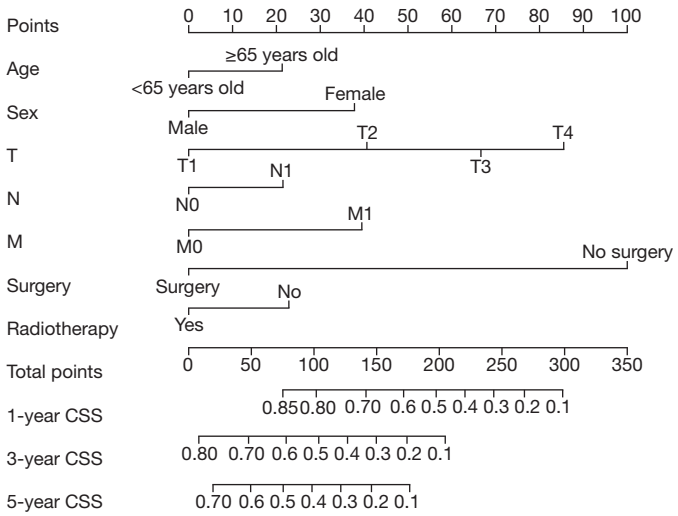

Figure 3 Nomogram anticipating the CSS of CC cases. CSS, cancer-specific survival; CC, colloid carcinoma.

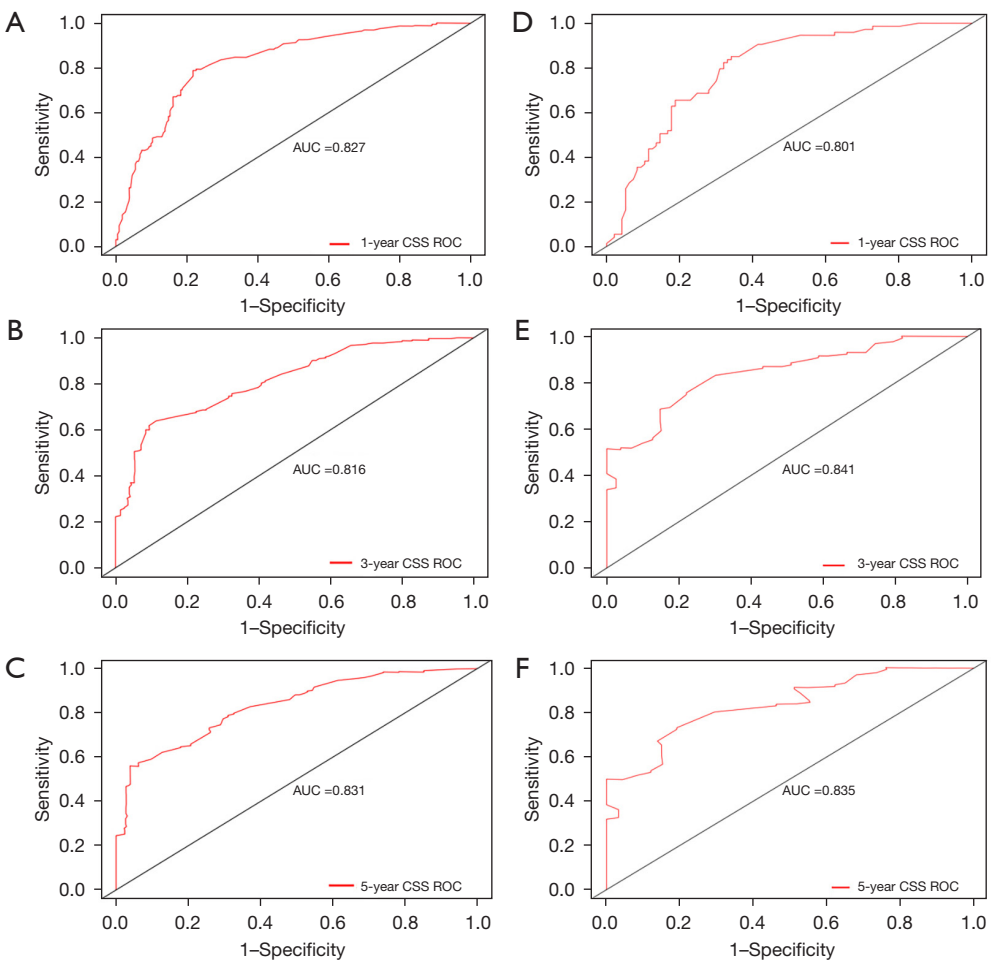

Figure 4 ROC curves for anticipating the 1-, 3-, and 5-year CSS of CC cases in the training cohort (A-C) and the validation cohort (D-F). AUC, area under the curve; CSS, cancer-specific survival; ROC, receiver operating characteristic curve; CC, colloid carcinoma.

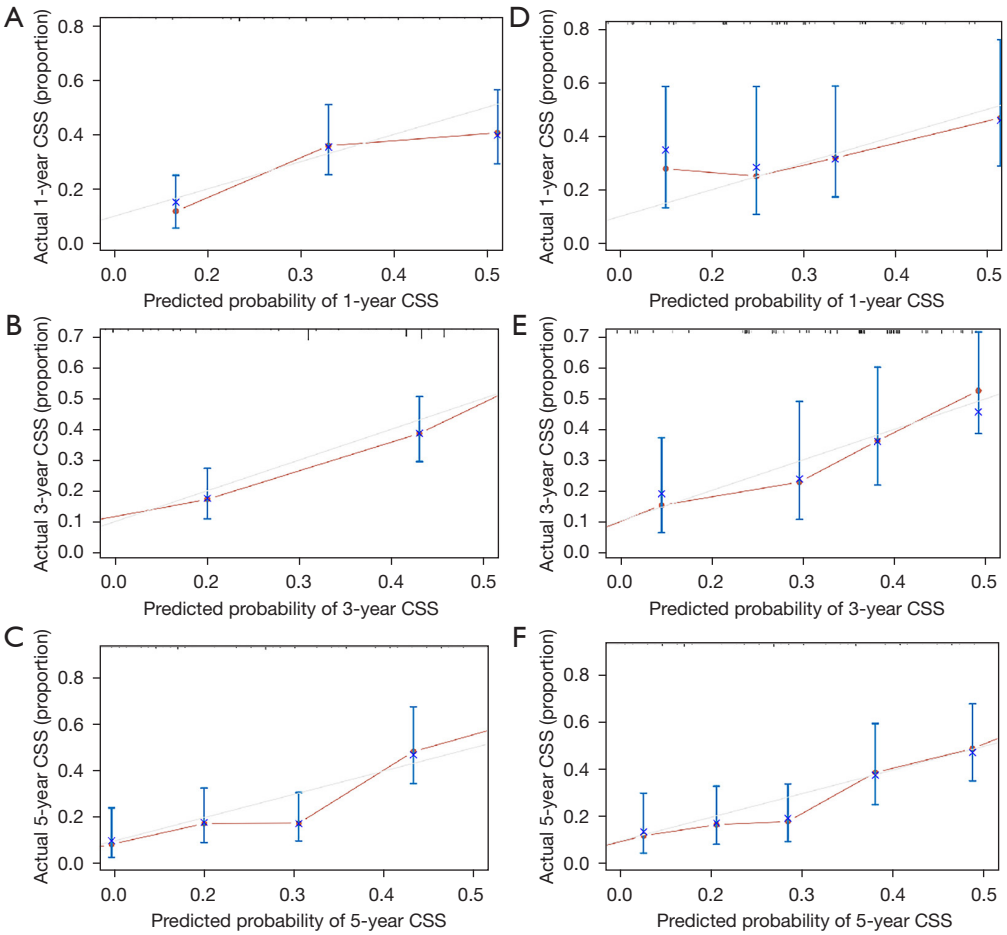

Figure 5 Bootstrap calibration of nomograms in the training cohort (A,C,E) and validation cohort (B,D,F). CSS, cancer-specific survival.

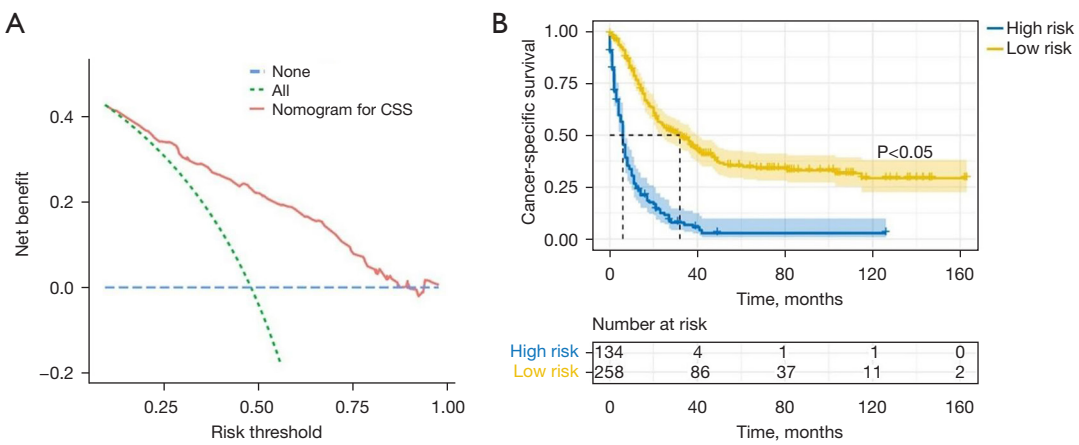

Figure 6 The DCA for predicting CSS in the training cohort (A) and survival analysis of CC cases in the training cohort after risk-stratification (B). CSS, cancer-specific survival; DCA, decision curve analysis; CC, colloid carcinoma.

13% to 83%, most medical experts believe that CC has a better prognosis than DAC (20,21). In a prior study, a 5-year survival rate of 57% for CC and 12% for resectable DAC was reported (6) while another study reported a survival rate of less than 10% for DAC (22). However, Seidel *et al.* (8) reported that the CC prognosis (5-year OS of 29%) was similar to that of DAC. The prognosis in 13 resected cases (median survival: 24 months, 5-year OS: 30%) was reported to be similar to that of DAC (23). However, these studies used small cohorts. According to our KM curves, the 1-, 3-, and 5-year survival rates of CC were superior to those of DAC, which were 20%, 40%, and 60%, respectively.

Since CC of the pancreas is uncommon, there are few thorough studies that cover its prognosis. Multivariate Cox regression analyses were carried out in this study. These analyses found that older age, being male, having more sophisticated TNM stages, not having surgery, and adjuvant radiotherapy were all independent factors that were significantly linked to worse CC outcomes and lower CSS rates.

Previous research has revealed that tumor size, lymph node metastases, vascular and nerve invasion, surgical margins, and immunohistochemistry expression of CC have little effect on the prognosis (6). Age, sex, TNM stage, tumor size, tumor site, tumor grade, surgery, and radiotherapy were all identified as determinants of CC prognosis in our study. In the multivariate Cox regression analysis, the prognosis for CC patients was shown to be worse with increasing age. One explanation could be that elderly patients suffer from more basic illnesses, whereas younger patients can undergo more thorough treatment and demonstrate better compliance during follow-up examinations (24). Additionally, in older patients with CC, organ senescence, combined with a decline in immunological function, results in a greater risk of tumor recurrence and lowers their survival rates. Meanwhile, the male sex was revealed to be a protective factor against CC. It is common knowledge that estrogen levels decline in postmenopausal women. According to articles published in The Lancet, estrogen deficiency raises the risk of pancreatic cancer (25,26). Most of our CC patients were elderly, and the elderly women were in menopause, which explains the high likelihood that male sex is a protective factor against CC.

TNM stages were independent risk factors for CC. Our findings showed that later stages were associated with a worse prognosis, which is in line with outcomes from prior research (13,27). Recent studies have reported that postoperative survival times are shorter for patients with poorly differentiated pancreatic cancer than those with well-differentiated pancreatic cancer. For instance, in a retrospective study of 396 cases of pancreatic cancer, Jeekel (28) observed that cases with well-differentiated cancer had a median survival duration of 35.5 months, while those with poorly-differentiated tumors had a median survival duration of 14.8 months. This is probably because tumors with less differentiation have more aggressive biology, which speeds up local and distant metastasis (29). In our study's univariate analysis, tumor differentiation was identified as a prognostic factor; however, it was not an independent factor in the multivariate analysis. The lymph node clearance rate is reported to be higher for the excision of lesions in the pancreatic head than in the pancreatic tail (17). The larger number of node dissections in our study for CC likely implicated the higher rate of CC in the pancreatic head. Current research is investigating whether more extensive lymph node dissection has a therapeutic benefit in CC (30). Early DAC should be considered a high-risk disease with increased potential for systemic metastasis and may require systemic treatment (15). Sakoda *et al.* (31) discovered that, like DAC, CC metastasis frequently occurs in the liver. In our study, the proportions of CC and DAC patients without distant metastases were 75.6% and 75%, respectively.

Surgery is the preferred treatment for pancreatic cancer. Because more than 90% of pancreatic cancer patients will experience local recurrence or distant metastases following surgery (32-34), adjuvant therapy is also essential. As per the National Comprehensive Cancer Network (NCCN) standards, DAC cases undergoing surgical treatment should get adjuvant chemotherapy regardless of their postoperative clinical conditions (35). Recently, it was discovered that preoperative chemotherapy was significantly correlated with enhanced median overall survival in DAC patients compared with those who received surgery as the first-line treatment (36). The most likely reason for this is that the R1 resection rate is 15–35% when patients initially undergo surgery, which has a negative influence on survival (37,38). A previous case report indicated that a patient with a 15-cm locally-invasive pancreatic colloid carcinoma tumor remained asymptomatic and had a good quality of life 24 months after surgery (9). It is supposed that the 5-year survival rate for CC following radical surgical resection was 60%; however, the significance of this outcome in CC is uncertain because the study did not examine the influence of postoperative adjuvant therapy. Another case report described gastrointestinal hemorrhage caused by CC, and surgical excision of the tumor may be advantageous (39).

Adsay *et al.* (6) analyzed 17 CC cases and found that 10 successfully underwent radical surgical resection with an 88% resection rate. After surgery, approximately half of the patients received no treatment, while four underwent both radiotherapy and chemotherapy, one underwent chemotherapy only, and one underwent radiotherapy only. Adjuvant chemoradiotherapy was found to be effective in patients with node-positive CC in another trial (40).

As shown above, there are no clear clinical guidelines for CC, which may be due to the small number of cases in these studies. In the present study, we noted that undergoing surgery and radiotherapy were crucial protective parameters for CC cases. However, chemotherapy was not an independent predictor of CC prognosis, which could be due to the SEER database's small number of CC cases. Therefore, extensive clinical studies are needed to evaluate the prognostic value of various chemotherapy approaches. Currently, there are no specific recommendations for the management of CC. Surgical intervention and postoperative radiotherapy are still required, even though CC has a better prognosis than DAC.

Prognostic nomograms are well-known and accepted simple models for determining prognosis, in which intricate mathematical representations of complex statistical models are used (41-43). Prognostic nomograms have also been shown to be more precise and thorough than other models, with clinical qualities that are simple to evaluate and easy to use in clinical practice. Here, a novel nomogram for forecasting the 1-, 3-, and 5-year CSS percentages for CC was developed and validated. The AUC values and all C-indices were greater than 0.75, indicating high accuracy. Additionally, there was good agreement between the calibration curve and the diagonal reference line.

However, there were some limitations to our study. First, since it was a retrospective study, there may have been selection bias. Therefore, multicenter, extensive, prospective studies should be carried out to confirm our observations and rule out any bias. Second, surgical procedures, radiation doses, particular chemotherapy regimens, and further clinical information could not be acquired because of the limited information accessible in the SEER database, which may have impacted the findings. Third, the CC and DAC cases were all from the United States, so the cohort may not have been representative of patients worldwide.

Conclusions

Our findings demonstrate that compared with DAC, CC is featured by better survival. We noted that age, sex, TNM stages, surgery, and radiotherapy were independent prognostic parameters of CC. We also developed a nomogram forecasting 1-, 3- and 5-year CSS rates for CC based on the above factors, which showed good discriminative ability and accuracy. This nomogram could provide tailored prognostic evaluations to surgeons and patients and also act as a source for treatment planning.

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Footnote

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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).

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