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Predictive and prognostic factors in pancreatic ductal adenocarcinoma

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Predictive and prognostic factors in pancreatic ductal adenocarcinoma

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Stage IA Patients With Pancreatic Ductal Adenocarcinoma Cannot Benefit From Chemotherapy: A Propensity Score Matching Study

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Purpose: Adjuvant chemotherapy following resection is recommended by clinical practice guidelines for all patients with pancreatic ductal adenocarcinoma (PDAC). This study aimed to evaluate the efficacy of adjuvant chemotherapy among the staging groups of the American Joint Committee on Cancer (AJCC) for PDAC.

Patients and Methods: This retrospective cohort analysis was performed by the Surveillance Epidemiology and End Results (SEER) (2004–2015) database and multi-institutional dataset (2010–2018). Baseline clinicopathologic characteristics of PDAC patients, including age, gender, ethnicity, marital status, education level, county income level, county unemployed rate, insurance status, grade, stage, chemotherapy, and radiotherapy, were collected. Overall survival (OS) was analyzed using the Kaplan–Meier method. The SEER and multi-institutional data were adjusted with 1:1 ratio propensity score matching (PSM).

Results: In total, 6,274 and 1,361 PDAC patients were included from the SEER database and multi-institutional dataset, respectively. Regardless of the count of resected lymph nodes, adjuvant chemotherapy prolonged the long-term OS time for stage IB, IIA, IIB, and III patients in both SEER and multi-institutional cohorts. Nevertheless, adjuvant chemotherapy did not provide additional clinical benefits even after a PSM adjustment for stage IA patients in both SEER and multi-institutional cohorts.

Conclusion: Adjuvant chemotherapy improved the long-term survival of stage IB, IIA, IIB, and III PDAC patients; however, it demonstrated no survival benefit in stage IA PDAC patients. Thus, adjuvant chemotherapy should not be recommended for stage IA PDAC patients. These would significantly reduce the economic burden of society and improve the life quality of stage IA PDAC patients.

Keywords: pancreatic ductal adenocarcinoma, overall survival, chemotherapy, Surveillance, Epidemiology, End Results (SEER), prognosis

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most challenging malignancies to treat, even though surgical technique and systemic therapy have improved over the past decades. Due to concealed pathogenesis and rapid progress, only a small minority of PDAC patients undergo an operation. Consequently, PDAC has a lethality of more than 95% and poor prognosis in most cases (1, 2). Clinical treatment options vary according to the severity of PDAC. Curative resection is considered the only approach to cure resectable PDAC patients. The emergence of neoadjuvant therapy offers the potential for curative resection in borderline resectable patients with initially unresectable and locally advanced PDAC (3). Postoperative adjuvant chemotherapy is still an essential supplementation to further improve the prognosis of PDAC patients (4) and is recommended for all patients with PDAC following resection according to the European Society for Medical Oncology-European Society of Digestive Oncology (ESMO-ESDO) and National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines (5, 6).

Despite all attempts made to improve the survival rate of PDAC patients, a meta-analysis including five randomized controlled trials showed that adjuvant chemotherapy only provided an extra 3 months of median survival time for patients with resected PDAC (7). Considering that adjuvant chemotherapy may cause pain, nausea, tiredness, drowsiness, and breath shortness, clinicians should be cautious about the application of adjuvant chemotherapy. It has been reported that adjuvant chemotherapy has no favorable impact on the survival of early-stage patients in many malignancies such as ovarian cancer (8), lung cancer (9), gallbladder cancer (10), and colorectal cancer (11). In the current study, we performed a population-based and multi-institutional analysis on PDAC patients to evaluate the efficacy of adjuvant chemotherapy with an ultimate aim to investigate whether adjuvant chemotherapy was necessary for early-stage PDAC patients.

MATERIALS AND METHODS

Ethics Statement

This study was approved by the institutional review board of The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University. Patients from the Surveillance, Epidemiology, and End Results (SEER) database had previously consented to participate in any scientific research worldwide.

Patients

We selected patients with PDAC from the SEER database (2004–2015) and multi-institutional dataset (2010–2018). In the SEER database, all the cases were identified by the topographical code of "pancreas" (International Classification of Disease for Oncology, third edition, ICD-O-3) using SEER*Stat software (Version 8.2.0). The multi-institutional dataset was from The Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University and Xuzhou Central Hospital, The Affiliated Xuzhou Hospital of Medical College of Southeast University. Inclusion criteria

TABLE 1 | Baseline clinicopathologic characteristics of PDAC patients.

Variables	SEER (n = 6,274)	Multi-institutional dataset (n = 1,361)
Age		
Median (range)	66 (26–93)	57 (19–74)
Gender		
Male	3,194 (50.9%)	649 (47.7%)
Female	3,080 (49.1%)	712 (52.3%)
Ethnicity		
White	5,174 (82.5%)	0
Black	666 (10.6%)	0
Asian[a]	0	1,361 (100%)
Other	434 (6.9%)	0
Marital status		
Married	3,936 (62.7%)	1,187 (87.2%)
Other[b]	2,338 (37.3%)	174 (12.8%)
Grade		
I + II	3,522 (56.1%)	882 (64.8%)
III + IV	2,271 (36.2%)	422 (31.0%)
Unknown	481 (7.7%)	57 (4.2%)
Stage		
IA	503 (8.0%)	158 (11.6%)
IB	1,193 (19.0%)	299 (22.0%)
IIA	449 (7.2%)	207 (15.2%)
IIB	2,555 (40.7%)	473 (34.8%)
III	1,574 (25.1%)	224 (16.5%)
Chemotherapy		
Yes	4,353 (69.4%)	747 (54.9%)
No/unknown	1,921 (30.6%)	614 (45.1%)
Radiotherapy		
Yes	2,466 (39.3%)	306 (22.5%)
No	3,808 (60.7%)	1,055 (77.5%)
County income level		
Low	703 (11.2%)	-
Mid-low	3,310 (52.8%)	-
Mid-high	1,619 (25.8%)	-
High	642 (10.2%)	-
Education level[c]		
Low	178 (2.8%)	127(9.3%)
Mid-low	1,250 (19.9%)	478 (35.1%)
Mid-high	3,101 (49.5%)	673 (49.5%)
High	1,745 (27.8%)	83 (6.1%)
Insurance status		
Insured	4,778 (76.2%)	-
Uninsured	139 (2.2%)	-
Other[d]	1,357 (21.6%)	-
County unemployed rate		
Low	648 (10.3%)	-
Mid-low	4,425 (70.5%)	-
Mid-high	1,166 (18.6%)	-
High	35 (0.6%)	-

[a] *Born and grown up in Asia.*
[b] *Including single, divorced, and widowed, etc.*
[c] *County education level for the SEER database and individual education level for the multi-institutional data.*
[d] *Including unknown and blank.*
PDAC, pancreatic ductal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results.

were as follows: (1) ≥18 years; (2) first primary PDAC with histological diagnosis; (3) without distant metastasis at diagnosis; (4) treatment with curative surgery; (5) definite number of resected lymph nodes; (6) definite staging groups according to the 8th Edition American Joint Committee on Cancer (AJCC) staging manual; and (7) definite information about radiotherapy and chemotherapy. Follow-up time ranged from 0 to 143 months in the SEER database and from 0 to 88 months in the multi-institutional dataset. Patients with unavailable follow-up information were excluded. The International Study Group on Pancreatic Surgery (ISGPS) recommended that at least 15 lymph nodes should be resected to assess the status of lymph nodes (12). Therefore, patients would be divided into two subgroups (15 or more lymph nodes evaluation, <15 lymph nodes evaluation) for further analysis. Baseline clinicopathologic characteristics of PDAC patients included age, gender, ethnicity, marital status, education level, county income level, county unemployed rate, insurance status, grade, stage, chemotherapy, and radiotherapy. Education level meant county education level in the SEER database. The variable "%< high school education (in tens) ACS 2011–2015" was used to evaluate the county education level in the SEER database, which was divided into quarters (low: <11.2, mid-low: 11.2–19.8, mid-high: 19.8–28.4, high: >28.4). Likewise, "median family income (in tens) ACS 2011–2015" variable was also divided into quarters (low: <5,300, mid-low: 5,300–7,700, mid-high: 7,700–10,150, high: >10,150), and "% unemployed ACS 2011–2015" variable was divided into quarters (low: <6.3, mid-low: 6.3–11.1, mid-high: 11.3–15.8, high: >15.8). Insurance status was classified as insured (including insured and any Medicaid), uninsured, and other (including unknown and blank). Notably, data for insurance status before 2007 were not available in the SEER database. In the multi-institutional dataset, education level meant individual education level and was divided into four levels: low (elementary school), mid-low (middle school), mid-high (university or college), and high (postgraduate).

Statistical Analysis

All data were analyzed by IBM SPSS 22.0 software. The survival curves for overall survival (OS) were drawn using the Kaplan–Meier method. OS was defined as the interval from PDAC diagnosis until death or the last follow-up. The SEER and multi-institutional data were adjusted with 1:1 ratio propensity score matching (PSM). $P < 0.05$ was considered statistically significant.

RESULTS

In total, 6,274 PDAC patients were selected from the SEER database, including 503 at stage IA, 1,193 at stage IB, 449 at stage IIA, 2,555 at stage IIB, and 1,574 at stage III (**Table 1**). The median age was 66 years, and the majority was White (82.5%) and reported as insured (including Medicaid). Patients with middle levels, including income level, education level, and unemployed rate, made up the majority of the entire cohort. A total of 3,522 (56.1%) patients had well or moderately differentiated tumors (grade I + II), and 2,271 (36.2%) patients had poorly differentiated or undifferentiated tumors (grade III + IV). Of

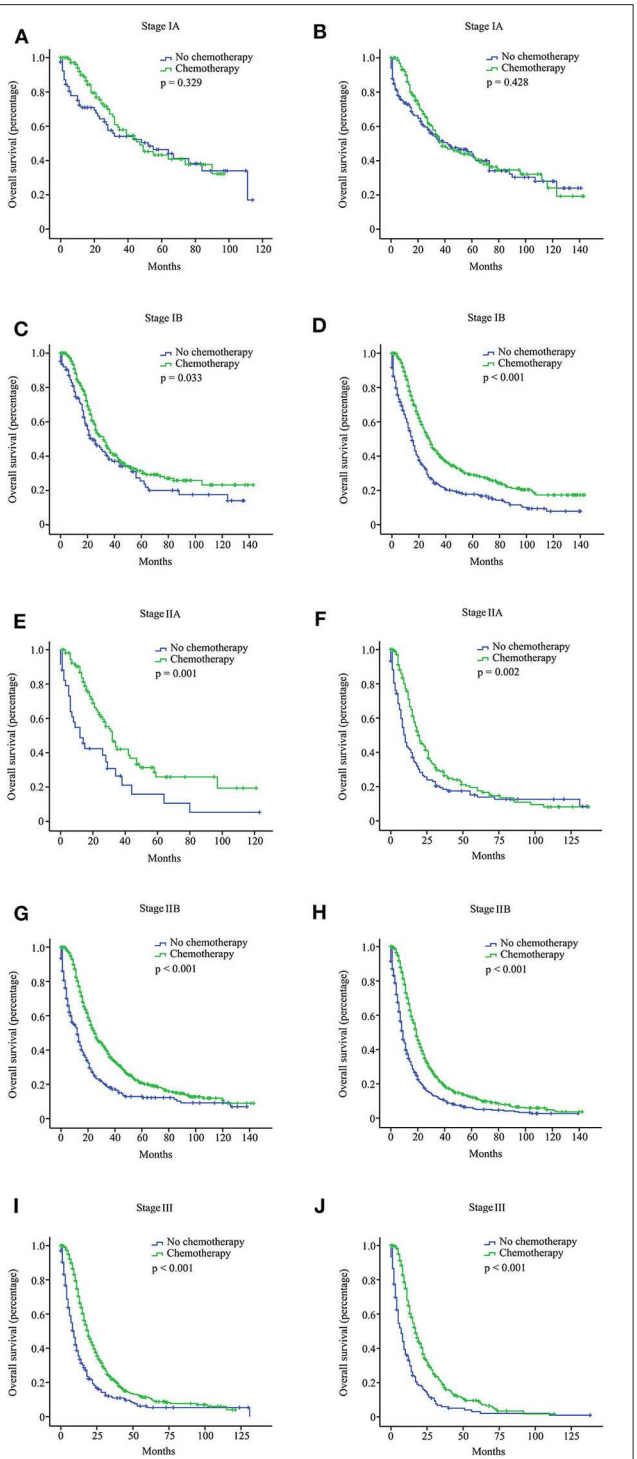

FIGURE 1 | Overall survival (OS) curves for pancreatic ductal adenocarcinoma (PDAC) patients with different stages from the Surveillance, Epidemiology, and End Results (SEER) database according to the 8th American Joint Committee on Cancer (AJCC) staging system. Stage IA with 15 or more resected lymph nodes **(A)**; stage IA with <15 resected lymph nodes **(B)**; stage IB with 15 or more resected lymph nodes **(C)**; stage IB with <15 resected lymph nodes **(D)**; stage IIA with 15 or more resected lymph nodes **(E)**; stage IIA with <15 resected lymph nodes **(F)**; stage IIB with 15 or more resected lymph nodes **(G)**; stage IIB with <15 resected lymph nodes **(H)**; stage III with 15 or more resected lymph nodes **(I)**; stage III with <15 resected lymph nodes **(J)**.

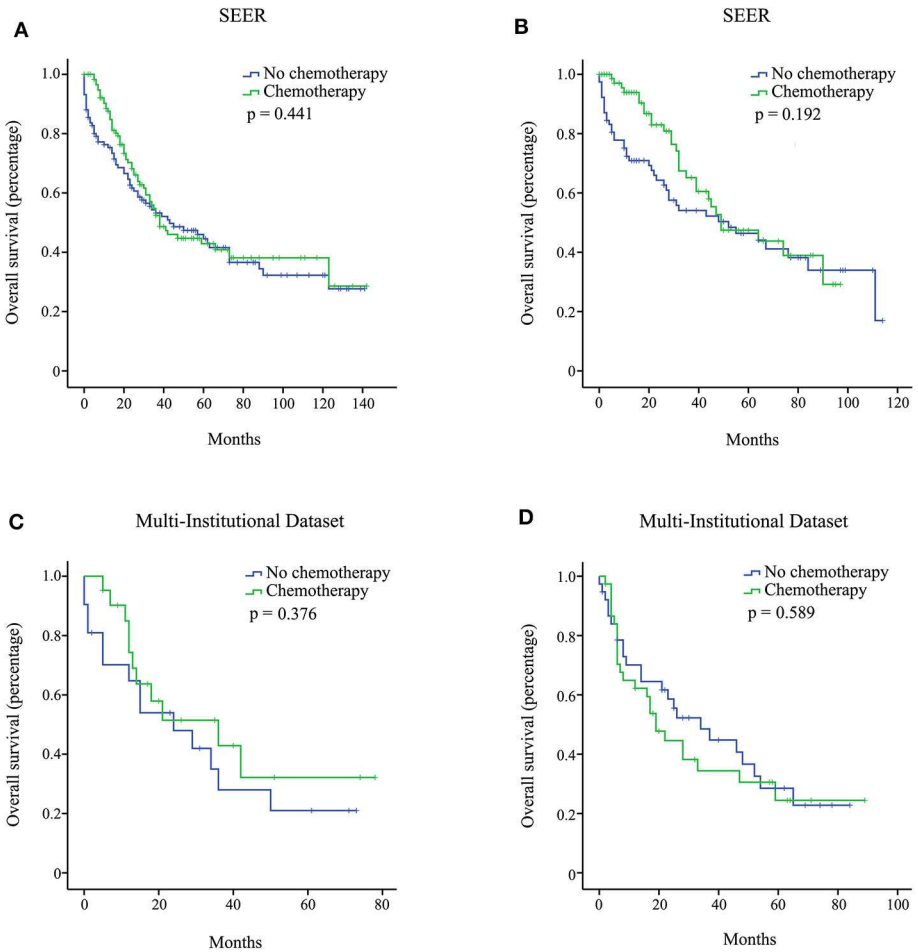

FIGURE 2 | Overall survival (OS) curves for stage IA pancreatic ductal adenocarcinoma (PDAC) patients from the Surveillance, Epidemiology, and End Results (SEER), and multi-institutional dataset after propensity score matching (PSM) adjustment. Stage IA with 15 or more resected lymph nodes from the SEER database **(A)**; stage IA with <15 resected lymph nodes from the SEER database **(B)**; stage IA with 15 or more resected lymph nodes from the multi-institutional dataset **(C)**; stage IA with <15 resected lymph nodes from the multi-institutional dataset **(D)**.

the entire cohort, less than half of the patients (39.3%) received radiotherapy. In addition, 4,353 (69.4%) patients received chemotherapy, while 1,921 (30.6%) patients did not.

We investigated the effect of chemotherapy on patients at each staging group from the SEER database (**Figure 1**). Regardless of the count of resected lymph nodes, chemotherapy prolonged the long-term OS time for stage IB, IIA, IIB, and III patients but not for stage IA patients. After PSM adjustment for clinically relevant covariates (including age, gender, grade, ethnicity, radiotherapy, and marital status), 117 pairs of stage IA patients with 15 or more resected lymph nodes and 78 pairs of stage IA patients with <15 resected lymph nodes were included in further analysis, respectively. As a result, there was still no survival difference between patients with chemotherapy and those without chemotherapy regardless of the count of resected lymph nodes ($p > 0.05$; **Figures 2A,B**). Additionally, we provided the cancer-specific survival (CSS) plots in **Supplementary Figure 1**. Similar results were observed. In particular, there was almost a statistically significant survival difference between patients with chemotherapy and those without chemotherapy for stage IB with 15 or more resected lymph nodes ($p = 0.054$).

In the multi-institutional dataset (**Table 1**), 1,361 PDAC patients met the inclusion criterion, including 158 cases at stage IA, 299 cases at stage IB, 207 cases at stage IIA, 473 cases at stage IIB, and 224 cases at stage III. The median age was 57 years, and all patients were Asian. A total of 882 (64.8%) patients had tumors at grade I + II, and 422 (31.0%) patients had tumors at grade III + IV. Among the patients, 77.5% did not receive radiotherapy. In addition, 747 (54.9%) patients received chemotherapy, while 614 (45.1%) patients did not. Similarly, the survival analysis showed that chemotherapy prolonged the long-term OS time for stage IB, IIA, IIB, and III patients but not for stage IA patients (**Figure 3**). After PSM adjustment, similar results were observed that chemotherapy did not provide clinical benefits for stage IA patients (**Figures 2C,D**).

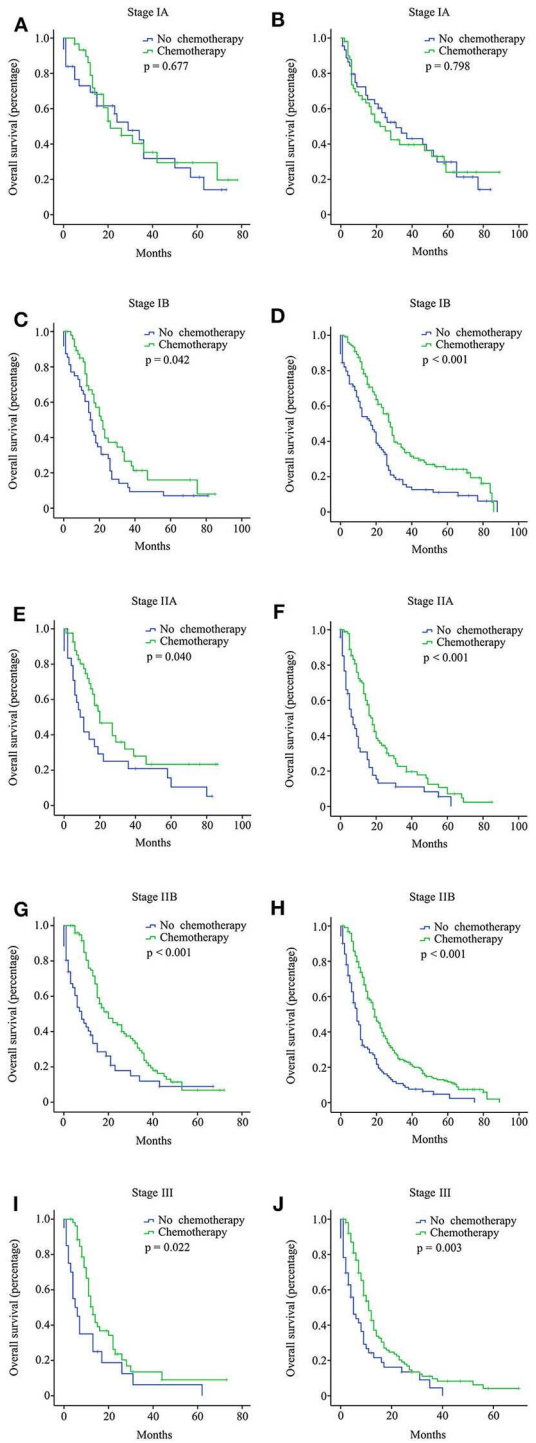

FIGURE 3 | Overall survival (OS) curves for pancreatic ductal adenocarcinoma (PDAC) patients with different stages from the multi-institutional dataset according to the 8th American Joint Committee on Cancer (AJCC) staging system. Stage IA with 15 or more resected lymph nodes **(A)**; stage IA with <15 resected lymph nodes **(B)**; stage IB with 15 or more resected lymph nodes **(C)**; stage IB with <15 resected lymph nodes **(D)**; stage IIA with 15 or more resected lymph nodes **(E)**; stage IIA with <15 resected lymph nodes **(F)**; stage IIB with 15 or more resected lymph nodes **(G)**; stage IIB with <15 resected lymph nodes **(H)**; stage III with 15 or more resected lymph nodes **(I)**; stage III with <15 resected lymph nodes **(J)**.

DISCUSSION

In this study, we analyzed the SEER and multi-institutional dataset to evaluate the influence of adjuvant chemotherapy on survival in PDAC patients with different staging groups and found that adjuvant chemotherapy demonstrated no survival benefit on stage IA PDAC patients but was conducive to improve the survival rate of patients with other stages (stages IB, IIA, IIB, and III). The result provided new evidence for individualized treatment and questioned the current recommendation in the ESMO-ESDO and NCCN clinical practice guidelines for early-stage PDAC patients. These would significantly reduce the economic burden of society and improve the life quality of patients.

Adjuvant chemotherapy provided survival benefits for PDAC patients indeed (13–15), which our study also supported. However, adjuvant chemotherapy seemed irrelevant to long-term survival for stage IA PDAC patients based on our analysis. Most studies reported resectable PDAC patients as a single unit for investigating the roles of adjuvant chemotherapy, including ESPAC-1, ESPAC-3, ESPAC-4, CONKO-001, and JASPAC-01 (4, 16–23). Few studies focused primarily on the early-stage PDAC patients. Hamura et al. (24) classified 81 cases of stage I PDAC patients into invasive subgroup and non-invasive subgroup according to whether there was tumor invasion around the pancreas. The study indicated that adjuvant chemotherapy may improve OS for the invasive subgroup but not for the non-invasive subgroup. According to the 7th edition AJCC staging manual, Ostapoff et al. (25) showed that adjuvant chemotherapy was associated with better OS outcomes for stage I PDAC (including stage IA and IB) using the National Cancer Data Base (NCDB). Also using the NCDB, however, Shaib et al. (26) further reported that adjuvant chemotherapy did not improve the prognosis for stage I sub-centimeter PDAC (<1 cm in greatest dimension). Although the classification methods in our study varied from the previous studies, these results indicated that early-stage PDAC patients may not benefit from adjuvant chemotherapy.

The difference in sensitivity to adjuvant chemotherapy between stage IA PDAC patients and PDAC patients with more advanced stages is likely rooted in genetic alterations. PDAC mainly arises from non-invasive pancreatic intraepithelial neoplasms (27), whose histologic progression (from hyperplasia, atypia, carcinoma *in situ* to invasive ductal adenocarcinoma) is highly correlated with the accumulation of genetic alterations (28). For instance, oncogenic *KRAS* mutation itself generates the earliest pancreatic hyperplasia (29), and its combination with inactivated *TP53* and *SMAD4* induces invasive carcinomas (29). Chromatin-remodeling complex *SWI/SNF* has also been revealed to drive the development of PDAC significantly (30). More epigenetic and genetic drivers of PDAC are being identified. However, it is still a riddle how the order of these mutations or abnormalities influence clinical presentation and disease outcome of PDAC. In 2015, Ortmann et al. (31) reported that the order in which *JAK2* and *TET2* mutations were acquired in patients with myeloproliferative neoplasms influenced clinical features and the response to

targeted therapy, which give us a hint that the sensitivity of PDAC at different stages to adjuvant chemotherapy may stem from the difference of key drivers and mutation order, which shape certain characteristics of early-stage and advanced PDAC.

A more backhanded reason may be the distinction of inner microenvironment of PDAC at different stages. As an inflammatory malignance, PDAC has exclusive pathological characteristics, with abundant cellular components, including cancer cells, pancreatic stellate cells (PSCs), cancer-associated fibroblasts, and tumor-associated macrophages, etc. (32). Varieties of cellular and molecular mechanisms are involved in tumor progression and resistance to chemotherapy. As PDAC progresses, both the proportion of each kind of cells and the extracellular matrix change. As opposed to PDAC patients at advanced stages which have complex components, such as the promotion of the angiogenesis, lymphangiogenesis, and induction of immunosuppressive reactions (33), early-stage PDAC patients mainly comprises of cancer cells and PSCs (34, 35). Upon adjuvant chemotherapy, the tumor microenvironment gets remodeled as each kind of cell reacts to the drugs (36–39). The difference in sensitivity to adjuvant chemotherapy between stage IA PDAC patients and PDAC patients with more advanced stages may be relevant to the complexity of tumor microenvironment and the various reactions of cells to chemotherapeutic drugs.

There are a few limitations in our study. First, the SEER database did not provide the data about recurrence, and the actual efficacy of the adjuvant chemotherapy could not be estimated fully. Second, the data of SEER and multi-institutional dataset were retrospective. More prospective analysis is necessary to validate the current conclusion. Third, detailed chemotherapy regimens were not recorded in the SEER database. Currently, most of the adjuvant chemotherapy regimens are based on gemcitabine (40) or fluorouracil (41). Other drugs such as oxaliplatin (42) and irinotecan (43) may be more suited to palliative treatment. In the study, all the chemotherapy regimens were regarded as a single unit, and it cannot be excluded whether a particular drug may play a favorable role in the prognosis of stage IA PDAC patients.

In sum, our analysis showed that current adjuvant chemotherapy demonstrated no survival benefit on stage IA PDAC patients, and their clinical treatment should be reevaluated accordingly.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/data/.

ETHICS STATEMENT

This study was approved by the institutional review board of The Affiliated Huaian NO. 1 People's Hospital of Nanjing Medical University. Patients from the Surveillance, Epidemiology, and End Results (SEER) database had previously consented to participate in any scientific research worldwide.

AUTHOR CONTRIBUTIONS

YZ and PW made substantial contributions to the design of the study, carried out the analysis, and interpreted the data. GX and MC contributed to the review of previous literature. ZC and MS contributed substantially to the data discussion and critically commented on the manuscript for scientific content. All authors made substantial contributions to data interpretation and drafting of the manuscript and were responsible for the quality of the overall manuscript, and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.01018/full#supplementary-material

Supplementary Figure 1 | CSS curves for PDAC patients with different stages from the SEER database according to the 8th AJCC staging system. Stage IA with 15 or more resected lymph nodes **(A)**; stage IA with <15 resected lymph nodes **(B)**; stage IB with 15 or more resected lymph nodes **(C)**; stage IB with <15 resected lymph nodes **(D)**; stage IIA with 15 or more resected lymph nodes **(E)**; stage IIA with <15 resected lymph nodes **(F)**; stage IIB with 15 or more resected lymph nodes **(G)**; stage IIB with <15 resected lymph nodes **(H)**; stage III with 15 or more resected lymph nodes **(I)**; stage III with <15 resected lymph nodes **(J)**.

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The Necessity of Dissection of No. 14 Lymph Nodes to Patients With Pancreatic Ductal Adenocarcinoma Based on the Embryonic Development of the Head of the Pancreas

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Objectives: Pancreaticoduodenectomy (PD) followed by lymphadenectomy is performed for patients with pancreatic ductal adenocarcinoma (PDAC) located in the head of the pancreas. Because the head of the pancreas could be divided into dorsal or ventral primordium in relation to embryonic development, the metastasis of lymph node (LN) may differ. In this retrospective study, we evaluated the impact of extended or standard LN dissection for PDAC located in ventral or dorsal primordia of the pancreatic head.

Methods: From February 2016 to November 2018, 178 patients who underwent PD for PDAC were enrolled at the Pancreatic Disease Center, Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University. According to the tumor location and the range of LN dissection, all patients were divided into three groups: ventral primordium with extended lymphadenectomy (VE group), ventral primordium with standard lymphadenectomy (VS group), and dorsal primordium with extended lymphadenectomy (DE group). Clinical and pathological features were retrospectively analyzed as were the long-term survival outcomes.

Results: More patients in the VE group were detected with metastasis in the lymph nodes around the superior mesenteric artery (LN14) than those in the DE group (LN along the right side of the superior mesenteric artery, LN14ab): 22.9 vs. 5.9%, $p = 0.005$; (LN along the left side of the superior mesenteric artery, LN14cd): 10.0 vs. 0.0%, $p = 0.022$. LN14 was involved in more patients in the VE group than in the VS group (22.9 vs. 5.0%, $p = 0.015$). For IIb-stage patients in the VE group, the overall survival time (18.3 vs. 9.3 months, $p < 0.001$) and disease-free survival time (12.2 vs. 5.1 months, $p = 0.045$) were longer in those with LN14cd (–) than those with LN14cd (+).

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Conclusion: This study suggested that patients with PDAC located in the ventral head of the pancreas had higher risk of LN14 involvement compared with those at dorsal. Thus, a thorough dissection of LN14 in PDAC located in the ventral head of the pancreas is recommended to optimize the regional extended lymphadenectomy.

Keywords: pancreas head cancer, pancreatic ductal adenocarcinoma (PDAC), pancreatic embryology, lymph node dissection (LN dissection), lymph nodes around superior mesenteric artery (SMA)

INTRODUCTION

Pancreatic cancer is a highly malignant digestive cancer with a median 5-years survival rate range from 2 to 9% (1, 2). Pancreatic ductal adenocarcinoma (PDAC) is the most frequent type, representing 60%−70% of pancreatic head neoplasms (3). Surgery is the main curative treatment for PDAC. Pancreaticoduodenectomy (PD) associated with standard or extended lymphadenectomy is recommended for patients with PDAC located in the head of the pancreas. Lymphadenectomy is an indispensable part in the curative pancreatic surgery, and lymph node (LN) metastasis has been recognized as one of the strongest prognostic factors. It has been shown that high-grade LN stage according to the American Joint Commission on Cancer (AJCC), 8th edition, predicts poor survival outcomes (4). The appropriate extent of lymphadenectomy to obtain a better prognosis has been the focus of clinical research.

The extent of standard lymphadenectomy of pancreatic head carcinomas includes the LNs station involved in two main routes of LN metastases: from the head of the pancreas to the common hepatic artery (CHA) then celiac axis and from the head of the pancreas to the superior mesenteric artery (SMA) (5). Furthermore, a previous study has demonstrated that PDAC located in the dorsal head of the pancreas are more likely to spread through the LNs of CHA and the hepatic duodenal ligament, and those located in the ventral head of the pancreas tended to spread through the LNs of SMA in relation to embryonic development (6).

The clarification of the profile of LNs, which are prone to metastasize according to the location of pancreatic head cancer, could help to optimize the surgical strategies and the prognosis of patients as well. Therefore, we conducted a retrospective study to investigate the lymphadenectomy strategies for PDAC in the head of the pancreas and their prognostic factors.

METHODS AND MATERIALS

Patients and Data Source

Five hundred twenty-eight patients who were included in a formed randomized controlled trial (NCT02787187), which was designed to verify the survival benefit of extended lymphadenectomy at the Pancreatic Disease Center, Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University from February 2016 to November 2018, were screened as follows. Inclusion criteria: (1) the carcinoma could be divided into either ventral or dorsal pancreatic head by a line that links the portal vein (PV)/superior mesenteric vein (SMV) and anterior edge of the intrapancreatic bile duct (**Figures 1**, **2**) (6). (2) Patients with a tumor located in the ventral pancreas had performed standard or extended lymphadenectomy and those with a tumor located in the dorsal pancreas underwent extended lymphadenectomy (**Figure 3**). (3) All patients were pathologically diagnosed with PDAC. (4) The neoplasms were resectable conforming to the consensus proposed by the National Comprehensive Cancer Network without neoadjuvant chemotherapy (7). Exclusion criteria were (1) the intraoperative surgical margin was positive.

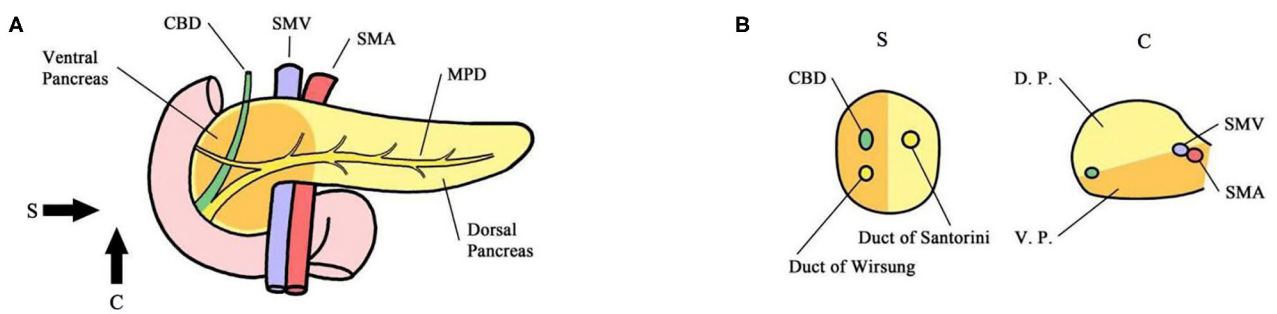

FIGURE 1 | (A) Sagittal view. **(B)** Coronary view. The pancreas is codeveloped from the ventral and dorsal primordium, which mainly constitute the body and tail of the pancreas and anterior partial head of the pancreas (yellow). The ventral primordium develops into the posterior part of the head of the pancreas that surrounds SMA/SMV. The head of the pancreas was divided into the ventral and dorsal pancreatic head by the line that links the portal vein (PV)/superior mesenteric vein (SMV) and anterior edge of the intrapancreatic bile duct. The main pancreatic duct of the common bile duct was located in the ventral pancreatic head, and the accessory pancreatic duct was located in the dorsal pancreatic head. *CBD* Common Bile Duct *MPD* Main Pancreatic Duct *SMA* Superior Mesenteric Artery *SMV* Superior Mesenteric Vein *DP* Dorsal Primordium *VP* Ventral Primordium.

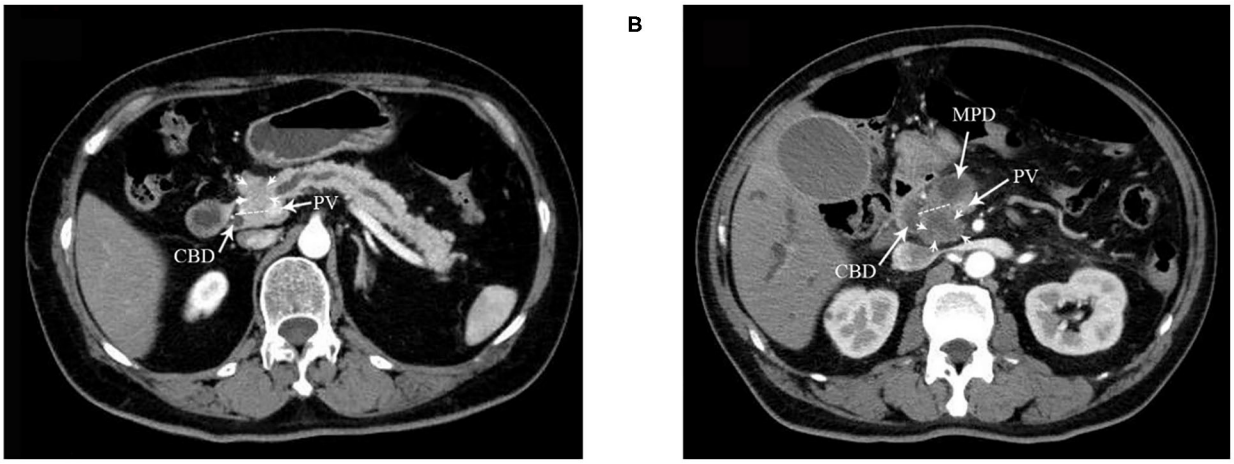

FIGURE 2 | A dotted line on the CT image indicates the boundary between the ventral and dorsal head of the pancreas in **(A,B)**. **(A)** DE group: tumor located in the dorsal head of the pancreas. CBD, common bile duct. PV portal vein. Arrows indicate the tumor. **(B)** VE and VS groups: tumor located in the ventral head of the pancreas. MPD, mean pancreatic duct. Arrows indicate the tumor.

(2) Distant metastases were confirmed intraoperatively. (3) Postoperative pathology confirmed the metastasis in para-aortic LN (LN16).

Finally, 178 patients were included in this study, including 70 patients with PDCA in the ventral primordium with extended lymphadenectomy (VE group), 40 patients with PDCA in the ventral primordium with standard lymphadenectomy (VS group), and 68 patients in the dorsal primordium with extended lymphadenectomy (DE group) (**Figure 4**).

Assessment of Tumor Progression

Tumor stage was assessed using the eighth edition of the American Joint Committee on Cancer (AJCC) classification (8). The Japan Pancreas Society's General Rules for the Study of Pancreatic Cancer (6th edition, 2009) for LNs station was applied (9).

Follow-Up Visit

Since discharge, follow-ups were performed with telephone interviews every 2 months, recording the time and location of recurrence and their survival. Disease-free survival (DFS) and overall survival (OS) time were calculated from the date of the operation to the date of tumor recurrence or death. The patients with tumor recurrence and death were considered as event data; patients with no tumor recurrence or death were classified as censored data. The patients lost to follow-up were classified based on the condition of the last follow-up.

Statistical Analysis

All statistical analyses were performed using SPSS statistical software (version 22). Continuous variables were expressed as means with standard deviation or as medians with range or as rates (percentage). Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the chi-square test and the Fisher exact test in case of small expected frequencies. For the survival analysis, DFS and OS rates were analyzed by the Kaplan-Meier method with comparison of the log-rank test. For all tests, $P < 0.05$ were considered significant.

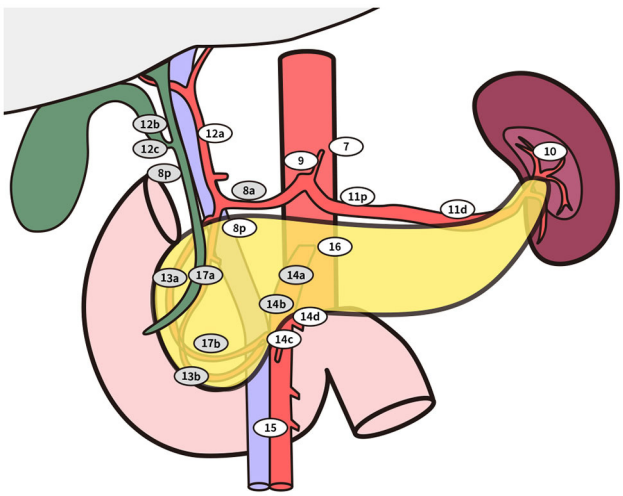

FIGURE 3 | Standard lymphadenectomy. No. 5 Supra pyloric lymph nodes; No. 6 infra pyloric lymph nodes; No. 8a lymph nodes in the anterosuperior group along the common hepatic artery No. 12b lymph nodes along the bile duct; No. 12c (located next to 12b), lymph nodes around the cystic duct; No. 13a lymph nodes on the posterior aspect of the superior portion of the head of the pancreas; No. 13b lymph nodes on the posterior aspect of the inferior portion of the head of the pancreas; No. 14a-b lymph nodes along right side of superior mesenteric artery No. 17a lymph nodes on the anterior surface of the superior portion of the head of the pancreas; No. 17b lymph nodes on the anterior surface of the inferior portion of the head of the pancreas. **Extended lymphadenectomy.** No. 8p lymph nodes in the posterior group along the common hepatic artery; No. 12a lymph nodes along the hepatic artery; No. 12p lymph nodes along the portal vein; No. 14c-d lymph nodes along the left side of superior mesenteric artery; No. 16 lymph nodes around the abdominal aorta besides standard range of lymph node dissection.

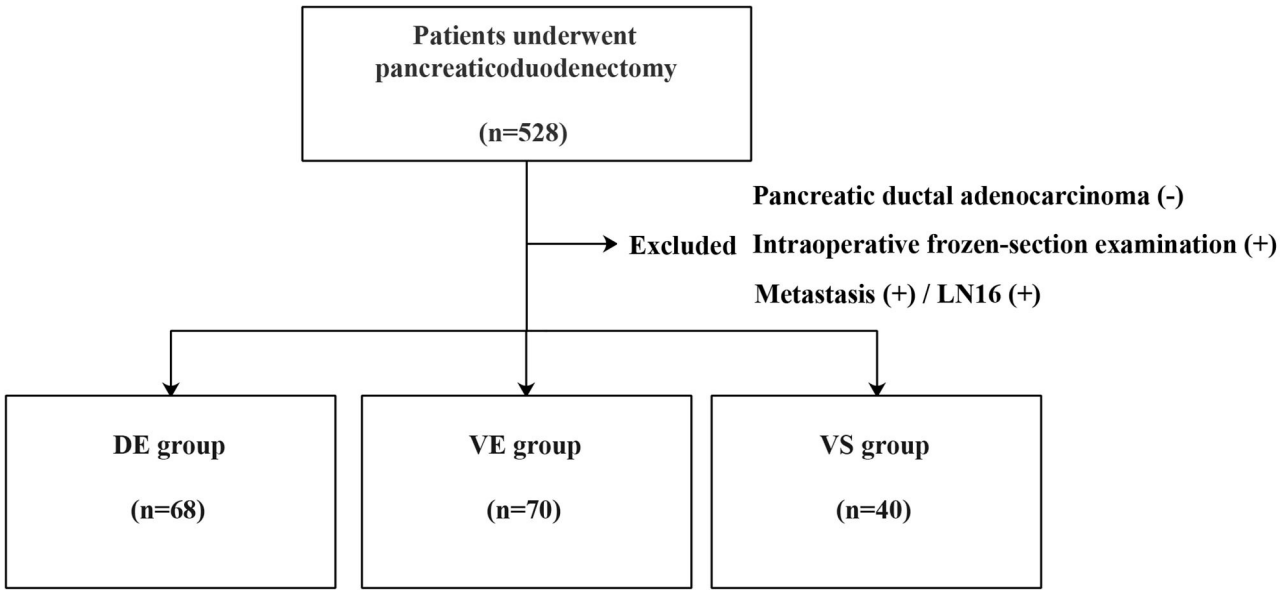

FIGURE 4 | Flow chart of inclusion: *DE* patients with tumor located in the dorsal head of the pancreas performed with extended lymphadenectomy; *VE* patients with tumor located in the ventral head of the pancreas performed with extended lymphadenectomy; *VS* patients with tumor located in the ventral head of the pancreas performed with standard lymphadenectomy.

RESULTS

Patient Characteristics

Of 178 patients included, 70 (39.3%) of patients were divided in the VE group, 68 (38.2%) in the DE group and 40 (22.5%) in the VS group. Patient demographic characteristics did not significantly differ among the three groups (**Table 1**), and neither did the preoperative tumor markers *including* carbohydrate antigen (CA) 19-9 and CA125. In preoperative imaging, common bile duct (CBD) dilation was identified significantly more frequently in the VE group (81.4 vs. 66.2%, $p = 0.041$) and the VS group (90.0 vs. 66.2%, $p = 0.006$) compared with the DE group (**Table 1**). Meanwhile there was no significant difference in the proportion of CBD dilation between the VE group and the VS group ($p = 0.232$). This was consistent with the previous study that carcinoma in the ventral head of the pancreas was more likely to lead to bile duct stenosis (6).

TABLE 1 | Patient characteristics.

Characteristics	DE group *n* = 68	VE group *n* = 70	VS group *n* = 40	*P*-value
PATIENT DEMOGRAPHICS				
Age, y	62 (44–84)	63 (35–85)	62 (42–87)	0.871
Sex, male	48 (70.6%)	44 (62.9%)	29 (72.5%)	0.489
PREOPERATIVE FACTORS				
Hb, g/L	126 (82–171)	127 (88–158)	125 (82–158)	0.983
PLT, 109/L	210 (71–435)	202 (73–383)	219 (98–390)	0.875
ALB, g/L	38 (24–50)	38 (26–51)	37 (29–54)	0.800
CA−199, U/mL	175.3 (0–17037)	156.9 (0–40200.0)	568.5 (0–8183.6)	0.696
CA−125, U/mL	15.3 (0.0–96.1)	16.3 (4.3–171.9)	27.8 (6.9–103.7)	0.385
TB, μmol/L	52.1 (6.6–407.8)	49.2 (6.2–416.4)	96.2 (7.0–292.4)	0.171
PBD	8 (11.8%)	5 (7.1%)	3 (7.5%)	0.594
Dilation of MPD	49 (72.1%)	44 (62.9%)	28 (70.0%)	0.487
Dilation of CBD①	45 (66.2%)	57 (81.4%)	36 (90.0%)	0.010

① *Further intergroup χ test: DE group vs. VE group 66.2% vs. 81.4%, p = 0.041; DE group vs. VS group 66.2% vs. 90.0%, p = 0.006; VE group vs. VS group 81.4% vs. 90.0%, p = 0.232. Hb, Hemoglobin; PLT, Platelet; ALB, Albumin; TB, Total Bilirubin; PBD, preoperative biliary drainage.*

Pathological Data and Tumor Stage

There was no significant difference in tumor diameter among the three groups (**Table 2**). Compared with the DE group, SMA in the VE group were more likely to be invaded (34.3 vs. 1.5%, $p = 0.000$), leading to a higher proportion of T4 tumor in the VE group than in the DE group (34.3 vs. 8.8% $p = 0.000$). There was no statistically significant difference in either SMA invasion or proportion of T4 tumor between the VE and VS groups (**Supplementary Table 2**). Patients in the DE group were associated with more portal vein (PV) invasion than the VE group (25.0 vs. 11.4%, $p = 0.039$). This may be related to the fact that the ventral pancreatic head tumor was more likely to be exposed to SMA in the anatomical position (6).

There were significant differences in LNs detected, LNs, and the proportion of patients in stage III among the three groups (**Table 2**). More LNs were detected (22.50 ± 8.10 vs. 17.28 ± 5.17, $p = 0.000$) and were confirmed positive LN (1.70 ± 1.81 vs. 1.09 ± 1.71, $p = 0.015$) in the VE group than those in the DE group (**Supplementary Table 1**). More LNs were detected in the VE group than those in the VS group (22.50 ± 8.10 vs. 19.07 ±

TABLE 2 | Pathologic variables.

Pathologic variables	DE group $n = 68$	VE group $n = 70$	VS group $n = 40$	*P*–value
Tumor size, cm	3.07 ± 1.16	3.19 ± 0.98	3.12 ± 0.96	0.700
SMA invasion	1 (1.5%)	24 (34.3%)	7 (17.5%)	0.000
CHA invasion	5 (7.4%)	3② (4.3%)	0 (0.0%)	0.092
SMV invasion	10 (14.7%)	19 (27.1%)	14 (35.0%)	0.045
PV invasion	17 (25.0%)	8 (11.4%)	2 (5.0%)	0.011
T STAGE				
T1	12 (17.6%)	8 (11.4%)	5 (12.5%)	0.547
T2	44 (64.7%)	29 (41.4%)	23 (57.5%)	0.020
T3	6 (8.8%)	9 (12.9%)	5 (12.5%)	0.795
T4	6 (8.8%)	24 (34.3%)	7 (17.5%)	0.001
N STAGE				
N0	39 (57.4%)	26 (37.1%)	20 (50.0%)	0.057
N1	23 (33.8%)	35 (50.0%)	15 (37.5%)	0.136
N2	6 (8.8%)	9 (12.9%)	5 (12.5%)	0.724
Total retrieved LNs	17.28 ± 5.17	22.50 ± 8.10	19.0 ± 5.91	0.000
No. positive LNs	1.09 ± 1.71	1.70 ± 1.81	1.35 ± 2.02	0.043
AJCC STAGE (8TH EDITION)				
IA	8 (11.8%)	6 (8.6%)	3 (7.5%)	0.720
IB	23 (33.8%)	12 (17.1%)	10 (25.0%)	0.079
IIA	3 (4.4%)	2 (2.9%)	3 (7.5%)	0.527
IIB	23 (33.8%)	22 (31.4%)	12 (30.0%)	0.910
III	11 (16.2%)	28 (40.0%)	12 (30.0%)	0.008
T4 (+) N2 (+)	0 (0.0%)	5 (17.9%)	0 (0.0%)	/
T4 (+) N2 (–)	5 (7.4%)	19 (27.1%)	7 (17.5%)	0.009
T4 (–) N2 (+)	6 (8.8%)	4 (5.7%)	5 (12.5%)	0.464

② *SMA was invaded by tumor at the same time for these three patients.*

TABLE 3 | Location of Lymph Node involvement in three groups.

LN no.	DE group $n = 68$	VE group $n = 70$	VS group $n = 40$	*P*-value
	Frequency of metastasis			
5	2 (2.9%)	1 (1.4%)	0 (0.0%)	0.980
6	1 (1.5%)	1 (1.4%)	0 (0.0%)	1.000
8a	3 (4.4%)	2 (2.8%)	1 (2.5%)	0.832
8p	1 (1.5%)	1 (1.4%)	/	1.000③
12	2 (2.9%)	3 (3.8%)	0 (0.0%)	0.423
12b + 12c	2 (2.9%)	1 (1.4%)	0 (0.0%)	0.980
12a + 12p	0 (0.0%)	1 (1.4%)	/	1.000③
13	12 (17.6%)	20 (28.6%)	12 (30.0%)	0.225
14④	4 (5.9%)	16 (22.9%)	2 (5.0%)	0.003
14ab	4 (5.9%)	11 (15.7%)	2 (5.0%)	0.003
14cd	0 (0.0%)	7 (10.0%)	/	0.022③
17	13 (19.1%)	12 (17.1%)	9 (22.5%)	0.789

③ *χ test between VE and DE group.*
④ *DE group vs. VE group: LN14: 5.9 vs. 22.9%, p = 0.005, LN14ab: 5.9 vs. 15.9%, p = 0.064, LN14cd: 0.0 vs. 10.0%, p = 0.022). VE group vs. VS group, LN14: 22.9 vs. 5.0%, p = 0.015.*

TABLE 4 | Perioperative risk and postoperative complications.

	DE group $n = 68$	VE group $n = 70$	VS group $n = 40$	*P*-value
Postoperative fatality	1 (1.7%)	0 (0.0%)	2 (5.0%)	0.637
Reoperation (DSA)	3 (4.4%)	1 (1.4%)	1 (2.5%)	0.565
Pancreatic fistula	8 (11.8%)	6 (8.6%)	1 (2.5%)	0.246
Biliary fistula	1 (1.5%)	2 (2.9%)	3 (7.5%)	0.234
Gastric fistula	2 (2.9%)	0 (0.0%)	3 (7.5%)	0.072
Intra-abdominal abscess	9 (13.2%)	10 (14.3%)	2 (5.0%)	0.312
Delayed gastric emptying	2 (2.9%)	1 (1.4%)	0 (0.0%)	0.506
Intra-abdominal bleeding	3 (4.4%)	2 (2.9%)	2 (5.0%)	0.829
Ascites	0 (0.0%)	2 (2.9%)	1 (2.5%)	0.386
Operation time, min	298 (150–720)	303 (120–480)	301 (120–600)	0.445
Intraoperative bleeding, ml	436 (50–1,500)	342 (50–1,200)	427 (50–3,400)	0.053
Intraoperative transfusion	46 (67.6%)	41 (58.6%)	26 (65.0%)	0.528

5.91, $p = 0.045$) (**Supplementary Table 2**). And more patients in the VE group were divided in stage III than those in the DE group (40.0% vs. 16.2%, $p = 0.002$) (**Supplementary Table 1**). There were no statistically significant differences in the rest aspects (**Supplementary Tables 1, 2**).

Location of Lymph Node Involvement

The peripancreatic LNs (LN13 and LN17) were the two main LNs involved in patients in these three groups. The proportion of LN14 metastases was significantly different among the three groups. Patients in the VE group were more likely to be involved with LN14 metastasis than patients in the DE group (22.9 vs. 5.9%, $p = 0.005$, in which LN14ab: 15.9 vs. 5.9%, $p = 0.064$, LN14cd: 10 vs. 0.0%, $p = 0.022$). The proportion of patients with LN14 metastasis was also significantly higher in the VE group than that in the VS group (22.9 vs. 5.0%, $p = 0.015$). There were no significant differences in LN metastasis in the rest of the locations. The positive rates of LN in each location of the three groups are shown in **Table 3**, **Supplementary Table 3**, and **Table 4**.

Three groups of patients with LN14 metastasis were further analyzed in **Supplementary Table 5** for details. In the 16 patients with LN14 metastasis in the VE group if only the LN14ab was dissected according to the standard LN dissection criteria, four (25.0%) patients with N1 stage would have been misclassified as N0. Besides, the preoperative characteristics and postoperative pathology of the VE group did not differ from those of the VS group except for the positive rate of LN14, suggesting that the LN dissection of the right side of SMA (LN14ab) may not be sufficient for patients with PDAC located in the ventral head of the pancreas.

Perioperative Risk

The postoperative mortality, reoperation rate, complications, duration of operation, intraoperative bleeding, and intraoperative transfusion of these three groups are shown in **Table 4**. In this study, three of the 178 patients experienced postoperative nosocomial death. Among them, one patient in the DE group died of pancreatic fistula in the ward on the 10th day after the operation. One patient in the VS group died of abdominal hemorrhage on the sixth day after the operation, and another patient in the VS group died due to SMA embolization on the seventh day after surgery. One patient in the VE group and three patients in the DE group received reoperation for postoperative hemorrhage, and one patient in the VS group who was suspected to be complicated with postoperative hemorrhage underwent laparotomy. There was no significant difference in the incidence of postoperative complications, including pancreatic fistula, biliary fistula, and delayed gastric emptying. Therefore, we propose that extended lymphadenectomy may not increase the perioperative risk.

Tumor Recurrence

Liver was the main site of tumor recurrence in the three groups. Although the proportion of patients with LN14 metastases in the VE group was higher than that in the other two groups, there was no significant difference in the rate of recurrence around SMA, which may be attributed to the thorough dissection of the surrounding SMA during the operation. The rest of the tumor recurrences are shown in **Table 5**, and there was no significant difference.

Survival Analysis

The rate of patients lost to follow-up was 2.7% with two patients in the VE group and one patient in the VS group. The minimal follow-up time was 15.4 months without tumor recurrence or death as censored data. The median follow-up time was 28.6 months.

In general, the range of lymph node dissection did not make statistical differences on the prognosis of 110 patients with tumor in the ventral head of the pancreas. The median survival time (MST) in the VS group was 17.0 months, the 1-year survival rate (1-YSR) was 67.5%, and the median disease-free survival time (MDFST) was 10.8 months. The MST in the VE group was 16.9 months, the 1-YSR was 67.1%, and the MDFST was 10.2 months. Except for the extent of LN dissection, the univariate survival analysis results show that preoperative albumin level, total bilirubin level, tumor marker, dilation of main pancreatic duct or common bile duct, preoperative biliary drainage, intraoperative vein reconstruction, N stage, and LN14 (±) did not make a difference on OS and DFS time (**Tables 6**, **7**) although the MDFST of patients with a T4 stage tumor was shorter than those with not-T4 stage (8.3 months vs. 12.7 months, $p = 0.020$). Further analysis showed that T4 stage was an independent prognostic factor of DFS [hazard ratio (HR) = 0.556, 95% confidence interval (CI): 0.337–0.918, $p = 0.022$].

Subgroup Analysis

In the subgroup of patients in the VE group with IIb stage, the OS time of patients with LN14cd (+) and the DFS time were both shorter than those with LN14cd (–) (OS: 9.3 months vs. 18.3 months, $p = 0.000$, DFS: 5.1 months vs. 12.2 months, $p = 0.045$; **Figure 5**).

DISCUSSION

Standard lymphadenectomy has been proven to prolong the 5-years survival rate of patients with PDCA in the head of the pancreas (10, 11), and it is the only criteria widely recognized by all at present (12). The necessity and the extent of extended

TABLE 5 | Recurrence pattern.

	DE group $n = 68$	VE group $n = 70$	VS group $n = 40$	*P*-value
RECURRENCE				
Residual pancreas	3 (4.4%)	2 (2.9%)	2 (5.0%)	0.829
SMA	2 (2.9%)	8 (11.4%)	2 (5.0%)	0.122
Liver	22 (32.3%)	33 (47.1%)	15 (37.5%)	0.198
Lung	3 (4.4%)	2 (2.9%)	1 (2.5%)	0.829
Bone	1 (1.4%)	1 (1.4%)	2 (5.0%)	0.411
Peritoneal seeding	8 (11.8%)	6 (8.6%)	3 (7.5%)	0.720
Retroperitoneal lymph node	4 (5.9%)	5 (7.1%)	2 (5.0%)	0.897
Others	0 (0.0%)	0 (0.0%)	1 (2.5%)	/

SMA superior mesenteric artery Others distal lymph node metastasis.

TABLE 6 | Prognostic factors in Univariate Analysis (OS).

	Univariate analysis			
	Patients (*n*)	mOS (month)	1-YSR (%)	*P*-value
OP extent, standard/extended	40/70	17.0/16.9	67.5%/67.1%	0.598
ALB,<35/≥35 g/L	26/84	18.0/16.6	80.8%/63.1%	0.266
TB,<24/≥24 μmol/L	40/70	21.7/15.2	70.0%/65.7%	0.064
Preoperative CA-199,<37/≥37 (U/ml)	24/86	21.716.3	70.8%/66.3%	0.319
Preoperative CA-125,<35/≥35 (U/ml)	87/23	16.8/21.1	67.8%/65.2%	0.940
Dilation of MPD, no/yes	38/72	20.8/16.6	68.4%/66.7%	0.057
Dilation of CBD, no/yes	17/93	25.4/16.5	82.4%/64.5%	0.162
PBD, no/yes	102/8	16.8/22.0	65.7%/87.5%	0.330
Portal vein /SMV resection, No/Yes	96/14	17.1/14.9	63.5%/92.9%	0.510
T stage T4, positive/negative	31/79	17.8/16.2	67.6%/67.1%	0.335
N stage, N0/N1/N2	44/52/14	18.0/14.8/23.2	70.5%/63.5%/71.4%	0.283
LN14-/LN14+	92/18	16.8/16.9	69.6%/55.6%	0.436

mOS median Overall Survival, mOS median overall survival, 1-YSR 1-year survival rate, OP operation, TB Total Bilirubin, PBD preoperative biliary drainage.

lymphadenectomy remain a fierce debate. A few prospective clinical studies found that extended lymphadenectomy did not contribute to survival (13–16), thus optimization of the lymphadenectomy to obtain an accurate LN stage of pancreatic head cancer and ensure the safety of the operation is a major challenge. The International Study Group on Pancreatic Surgery (ISGPS) proposed a standard lymphadenectomy based on the positive rate of each LN station involved and the related prognostic significance (12). The dissection of regional LNs around the SMA remains controversial. As reported previously, LN14ab was associated with early recurrence (17), and the skeletonization of the right side of SMA contributed to isolate the uncinate during operation although skeletonization of the left side of SMA may significantly increase the surgical risk and the incidence of severe complications (18, 19). Therefore, dissection of LN14cd is not recommended in general.

TABLE 7 | Prognostic factors in Univariate and Multivariate Analysis (DFS).

	Univariate analysis			Multivariate analysis		
	Patients (*n*)	**mDFS (m)**	***P*-value**	**HR**	**95% CI**	***P*-value**
OP extent, standard/extended	40/70	10.8/10.2	0.108			
ALB⑤, <35/≥35 g/L	26/84	/	/			
TB, <24/≥24 μmol/L	40/70	9.4/11.1	0.275			
Preoperative CA-199, <37/≥37 (U/ml)	24/86	14.4/10.0	0.189			
Preoperative CA-125, <35/≥35 (U/ml)	87/23	10.6/10.4	0.639			
Dilation of MPD, no/yes	38/72	12.8/10.5	0.774			
Dilation of CBD, no/yes	17/93	9.1/11.3	0.092			
PBD, no/yes	102/8	10.7/12.7	0.784			
Portal vein /SMV resection, No/Yes	96/14	11.7/8.7	0.109			
T stage T4, positive/negative	31/79	8.3/12.7	0.020	0.556	0.337–0.918	0.022
N stage, N0/N1/N2+	44/52/14	12.8/9.4/9.7	0.285			
LN14-/LN14+	92/18	11.0/9.1	0.191			

⑤ *More than 50% of data is censored. mDFS median disease-free survival time, HR Hazard Ratio, CI Confidence Interval.*

This research suggests that the LN on both sides of SMA (LN14ab and LN14cd) should be thoroughly dissected for patients with resectable PDAC located in the ventral head of the pancreas, and for those with PDAC located in the dorsal head of the pancreas, only LN14ab should be dissected as the standard procedure.

First, the LN reflux of the head of the pancreas may circulate in different ways. Kitagawa et al. (6) proposed that the lymphatic pathways of the pancreatic head of different embryonal origin were not identical, and the tumors in the ventral head of the pancreas were more likely to metastasize to the LN14 although Okamura et al. (19) found that the positive rate of LN14 did not differ according to the embryonic segment of the head of the pancreas. The conclusion had certain limitations because the study excluded patients with tumor size >4 cm, and its study subjects were mainly patients with stage IIA and IIB. Besides the positive rate of LN14 was recorded as a whole instead of separating into LN14ab and LN14cd.

In this study, the pathological stage of 178 patients included varied from stage I to III according to current clinical guidelines. The results show that the number of positive LNs detected in the VE group was significantly higher than that in the DE group, and the difference was mainly contributed by the higher

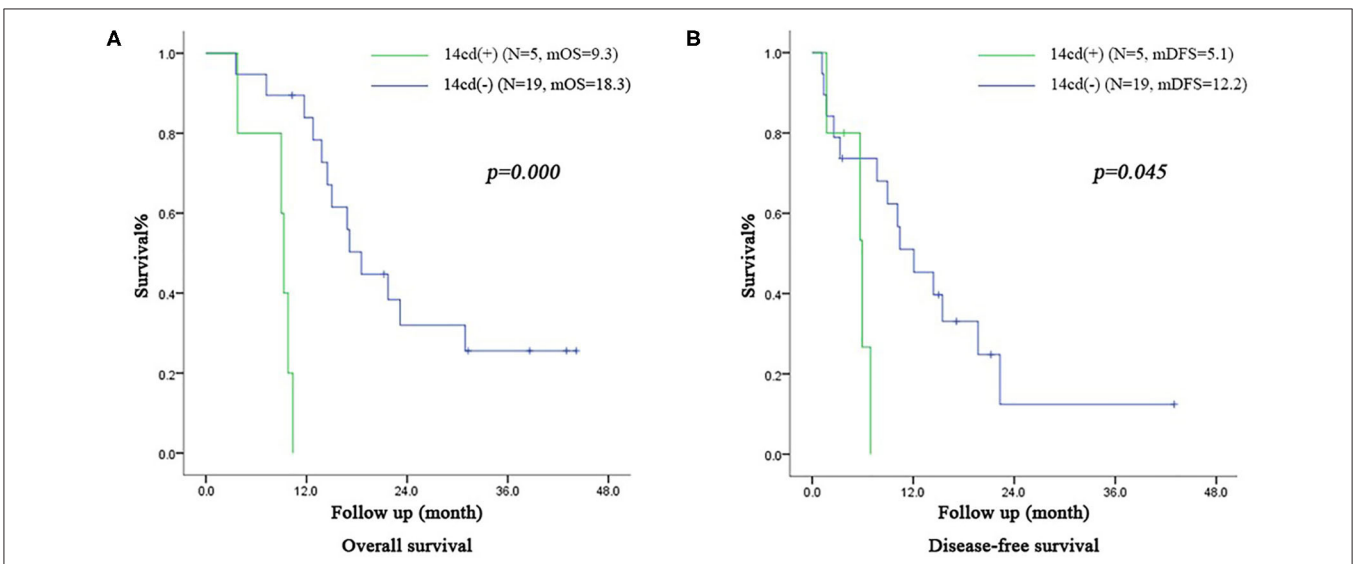

FIGURE 5 | (A) Survival curve of subgroup (patients with IIb stage including LN(+) by direct tumor extension in VE group) according to the LN14cd (±), *mOS* median overall survival **(B)** Disease-free survival curve of subgroup (patients with IIb stage including LN(+) by direct tumor extension in VE group) according to the LN14cd (±), *mDFS* median disease-free survival.

positive rate of LN14ab and LN14cd. With similar preoperative characteristics, the positive rate of LN14 was higher in the VE group compared with the VS group, and the rest were not significantly different. Furthermore, four of 16 patients in the VE group with LN14 metastasis would have been misclassified as N0 without LN dissection, including LN14cd. Meanwhile, patients with isolated LN14cd metastasis were found in previous studies (20). As a conclusion, this study suggests that there would be a high risk of both LN14ab and LN14cd metastasis in patients with PDAC located in the ventral head of the pancreas. Thus, positive LN14cd may be missed under standard lymphadenectomy with dissection of LN14ab, leading to the inaccurate tumor stage and the overestimation of prognosis.

In addition, corresponding to a recent study by Kenjiro et al. (21) proposing LN14cd metastasis as an independent risk factor for prognosis, the survival analysis of this study also suggests that LN metastasis in LN14cd would be an adverse prognostic factor for IIb patients with PDAC located in the ventral head of the pancreas. Because LN14cd was out of the range for standard lymphadenectomy and not commonly dissected during PD, few studies were concerned with LN14cd metastasis in pancreatic head cancer. The survival benefit of LN14cd dissection or prognostic value of LN14cd metastasis were not so clear as para-aortic lymph node (LN16), which was defined as the third station LNs according to the definition of the Japan Pancreas Society, equivalent to distant metastases and previous randomized controlled trials (RCT) pointed out that patients could not benefit from dissection of LN16 (22, 23). Other studies suggest that patients with LN16 metastasis confirmed during surgical exploration undergo neoadjuvant treatment instead of continuing exploration (24). To better understand the prognostic effect of LN14cd, further studies, including larger number of patients, especially those with ventral pancreatic head cancer with LN14cd dissection, would be needed.

Although patients with borderline tumor (T4 stage) were shown to benefit from neoadjuvant therapy with prolonged survival time, these patients may develop complications that may contradict with surgery, and tumors unresponsive to neoadjuvant therapy may become unresectable (25–28). Thus, the optimal treatment strategies for borderline tumor of the head of the pancreas are still under discussion. We propose that the necessity of LN14cd dissection for borderline PDAC needs to be further validated.

However, this retrospective study also has some limitations. Fewer patients were included in the VS group in this study than those in the VE group and the positive rate of LN14cd was low, which led to selection bias. Second, a more precise criteria to divide tumor by imaging according to embryonic origin would be explored. A larger number of patients should be included to further elucidate the prognostic effect of LN14cd.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ruijin Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LQ, JuX, and ZX: study conception, drafting, and writing of the manuscript, tables. LQ, ZX, and WW: design and drawing figures. LQ, JuX, XD, HC, WC, and JiX: acquisition of data. LQ, JuX, ZX, CP, HL, and WW: analysis of data. JiX, WW, and BS: critical revision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Pros and Cons: High Proportion of Stromal Component Indicates Better Prognosis in Patients With Pancreatic Ductal Adenocarcinoma—A Research Based on the Evaluation of Whole-Mount Histological Slides

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The study aimed to investigate the potential of tumor–stroma ratio (TSR) on digitalized whole-mount histopathology to predict prognosis in patients with pancreatic ductal adenocarcinoma (PDAC). The effectiveness were evaluated through internal validation. Data were retrospectively collected from consecutive patients who underwent primary pancreatic resection from December 2016 to August 2017 (developing cohort) and from September 2017 to April 2018 (validation cohort). Digitalized whole-mount slide images were used to evaluate TSR by both pathologists and a computerized model based on Conditional Generative Adversarial Model (cGAN), respectively. TSR>1 and ≤1 denoted low and high stromal component. Logistic regression analysis revealed intratumoral necrosis and R1 independently associated with low stromal component in the developing cohort. Cox regression analysis revealed tumor–node–metastasis (TNM) stage [II vs. I: hazard ratio (HR), 2.584; 95% CI, 1.386–4.819; $P = 0.003$; III vs. I: HR, 4.384; 95% CI, 2.285–8.411; $P < 0.001$], stromal component (low vs. high: HR, 1.876; 95% CI, 1.227–2.870; $P = 0.004$), tumor grade (G3 vs. G1/2: HR, 2.124; 95% CI, 1.419–3.179; $P < 0.001$), and perineural invasion (with vs. without: HR, 2.147; 95% CI, 1.187–3.883; $P = 0.011$) were independent prognostic factors in the developing cohort. Stromal component categories could classify patients into subgroups within TNM stages I, II, and III based on over survival. All results were validated in the validation cohort. The weighted kappa value for categorical assessments between pathologists' evaluation and computer-aided evaluation was 0.804 (95% CI, 0.573–0.951). TSR represents a simple and reliable metric for combining the prognostic value of TNM stage in patients with PDAC.

Keywords: pancreatic ductal adenocarcinoma, prognosis, tumor–stroma ratio, whole-mount histological slides, patient stratification

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death worldwide, with a 5-years survival rate of ∼9% (1). Tumor staging systems are essential for categorizing patients into different risk groups based on prognostic factors and for guiding therapeutic approaches. However, the tumor–node–metastasis (TNM) staging system does not provide substantial predictive value. The median overall survival (OS) of patients in the same stage widely varies among different substages (2), which may be attributable to the heterogeneity of tumor cells and stroma (3). One could argue that some subpopulations could possibly benefit in terms of prognosis. To identify such potential groups, predictive parameters are necessary.

As the stroma encasing the malignant epithelial cells in pancreatic masses constitutes up to 80–90% of the tumor bulk, the stroma is now considered fundamental for tumor progression and drug delivery (4). Moreover, one recent study highlights the importance of stromal component for understanding tumor cell heterogeneity, as well as the role of these interactions in shaping tumor architecture and patient prognosis (5). Consistent with this principle, the amount of intratumoral stroma may be associated with prognosis (6). This prognostic parameter, which is also referred to as the tumor–stroma ratio (TSR), entails a simple microscopic quantification of the amount of intratumoral stroma on a tumor tissue slide, which is derived after surgical resection. Nevertheless, there exist some discrepancies in the prognostic impact of TSR in patients with PDAC. Using Masson trichrome staining or α-smooth muscle actin (α-SMA) staining in surgical specimen sections to evaluate stromal proportion, Shi et al. reported that a stromal proportion of ≤60% was of benefit for prognosis in PDAC (7). Heid et al. demonstrated that low tumor cellularity with a cutoff value of 30%, which was equivalent to a high amount of stroma, indicated better prognosis (8). Recently, a previous study has shown that TSR has no prognostic value in PDAC (9). The inconsistent conclusion drawn by these studies could be explained by the method for evaluating stromal proportion that only took the local part of the entire tumor into account, such as a single moderate magnification (10×) field with all four corners of the vision field located within the tumor (9), which was extensively used in colorectal cancer (10, 11) and other digestive tumors (12, 13). However, PDAC is characterized by a prominent feature of extensive desmoplasia (14), and evaluating the stromal proportion for the local part of the tumor may not be sufficiently accurate to estimate prognosis. Additionally, Torphy et al. analyzed the standard multiphase CT images of the whole tumor and indicated the correlation of high stromal component with favorable outcome in resected cases (15). By evaluating all tumor slides for the stromal proportion, Attiyeh et al. found that tumors with ≤50% stroma ($n = 21$) harbored significantly more altered genes than those with >50% stroma ($n = 14$) (16). Therefore, evaluating the stromal component for the whole tumor may clearly clarify the effect of stromal component on the prognosis of patients with PDAC.

Due to the limitations of previously used cohorts, the results of stromal component evaluation for the whole tumor were not credible enough for clinical practice. Hence, it is necessary to thoroughly investigate the predictive value of TSR for prognosis. We have routinely performed a standardized pathological examination with digitalized whole-mount slide images (DWMSIs) to facilitate TSR evaluation by semi-quantification. We hypothesized that patients with low TSR or high stromal component had better prognosis and that TSR, in addition to the TNM classification, could be a candidate marker to further stratify patients into more specific risk groups. Therefore, this study aimed to investigate the potential of TSR to predict prognosis in patients with PDAC.

METHODS

Study Population and Data Collection

A total of 440 consecutive patients with a final histopathological diagnosis of PDAC who underwent primary pancreatic resection at the Department of Hepatobiliary Pancreatic Surgery in Changhai Hospital (Shanghai, China) were enrolled for this study. Grading and staging were performed in accordance with the WHO recommendations (17) and the 8th edition of the AJCC staging system at the time of cohort generation. Clinical and follow-up data were obtained from a prospective digital database. For each patient, the observation period started with the surgical resection. With respect to the inclusion criteria, patients who underwent (1) surgery with curative intent and (2) a standardized pathological protocol for the resected specimen were included in this study. The exclusion criteria for this study were as follows: (1) patients with intraoperative metastasis (excluded lymph node metastases) or macroscopic evidence of margin involvement (R2); (2) patients who received neoadjuvant chemotherapy or radiotherapy; (3) patients with other malignancies in the past; (4) patients who died within 90 days; and (5) patients who failed to be followed up. Subsequently, 400 patients in total were included; of these patients, 207 who underwent primary pancreatic resection from December 2016 to August 2017 composed the developing cohort and 193 who underwent primary pancreatic resection from September 2017 to April 2018 composed the validation cohort. This study was approved by the Institutional Review Board of Changhai Hospital, and no additional informed consent was required to review the patients' medical records.

Pathological Examination

The Leeds Pathology Protocol was routinely used for pathological examination (18). The entire specimen was sliced into 5-mm-thick sections, resulting in 10–35 (average, 24.5 ± 6.7) formalin-fixed paraffin-embedded (FFPE) blocks for each specimen. Subsequently, each FFPE block was cut into 4-μm-thick sections on whole-tissue glass slides measuring 7.8 × 5.4 cm^2. Slides stained with hematoxylin and eosin (H&E) were scanned using a Hamamatsu S60 whole slide scanner (Hamamatsu Photonics, Hamamatsu City, Japan) to obtain digitalized whole-mount slide images (DWMSIs) with an average file size of 6.47 GB (19). DWMSIs could also be observed using NanoZoomer Digital Pathology view2 software version 2.7.25. The TSR was determined in all patients with available DWMSIs. On DWMSIs in which a tumor was identified at 200× magnification, the

percentages of epithelial and stromal components were semi-quantitatively assessed using the mean value of medium power fields at 100× magnification of the entire tumor scope on all DWMSIs (range, 2–3) of a given tumor. The TSR was estimated at 5/5, 6/4, 7/3, 8/2, 9/1, and so on. The TSR was scored independently by two senior pathologists, and any disagreement between these pathologists was resolved by discussion. We had determined "5/5 (1)" to be the best cut-off value of TSR for prognosis discrimination; hence, TSR >1 denoted low stromal component, whereas TSR ≤ 1 indicated high stromal component.

Computer-Aided Evaluation

The DWMSIs of 41 patients from the validation cohort were used for automated TSR evaluation with each region of interest (ROI) in a DWMSI mostly included epithelium, stroma, and background/other tissues components. These components were manually delineated by pathologists for each DWMSI in the training set. The training patches were subsequently generated from each DWMSI with non-overlapping sliding windows of 512X512 pixel sliding across each ROI (19). The training patches were then fed into deep semantic segmentation model based on conditional generative adversarial networks (cGAN) (20, 21) for training. The parameters were fixed after the training procedure and then were used in the validation cohort of DWMSIs (n = 41). After inferencing on patches of validation cohort, the segmentation result of patches was combined in consideration of the ROI (**Supplementary Figure 1**). For each patient, the pixel area of the epithelium and stroma region was computed in ROI and the TSR was then be calculated. As pathological examination shown, TSR >1 denoted low stromal content, whereas TSR ≤1 indicated high stromal content.

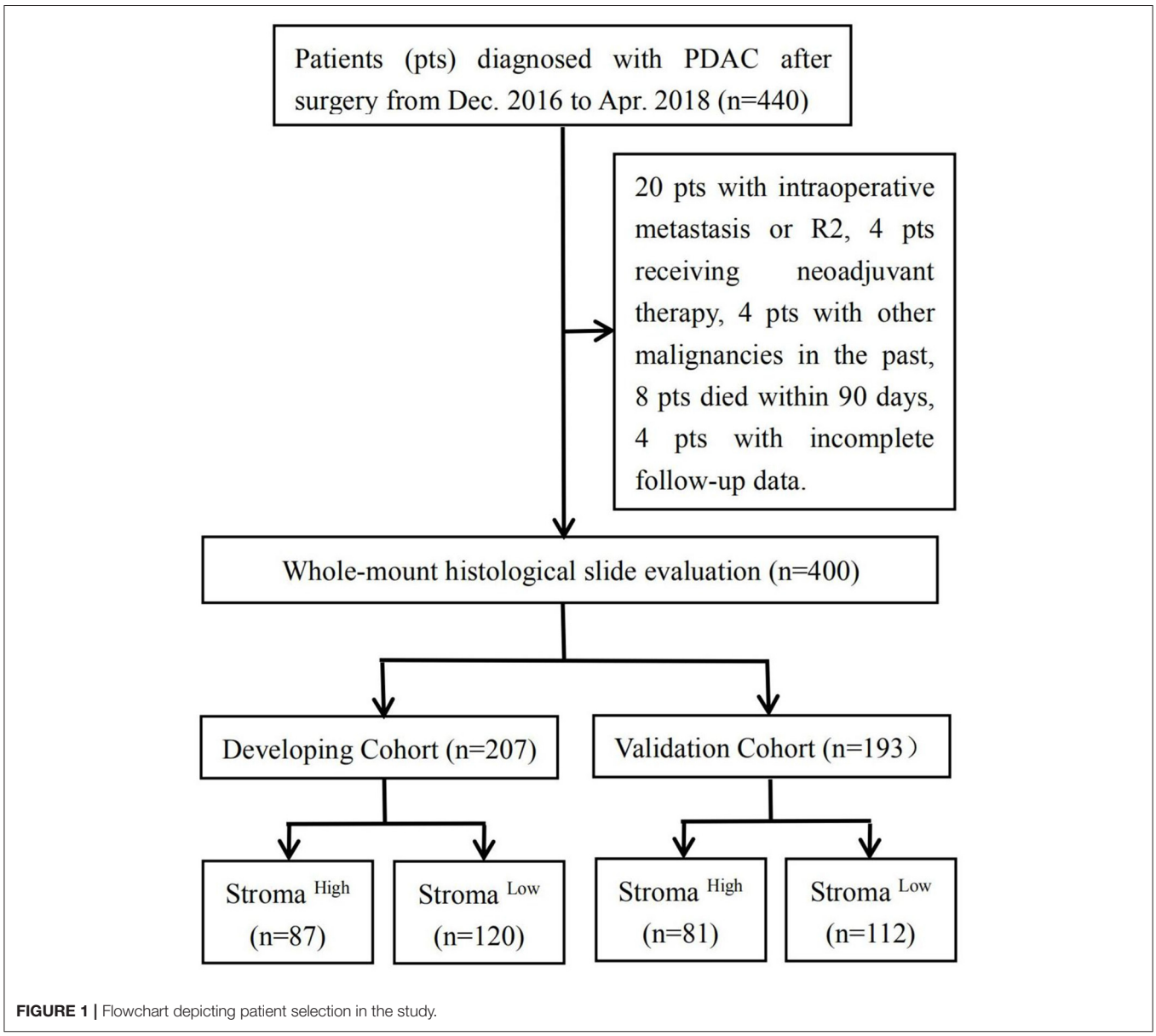

FIGURE 1 | Flowchart depicting patient selection in the study.

Follow-Up Protocol

The institutional follow-up was jointly completed by department follow-up specialists, and the third-party professional data were provided by LinkDoc Technology Co. Ltd. (Beijing, China). The frequency of follow-ups is done once per month during the first half year after operation, followed by once per quarter till 30th, April, 2020, the cut-off date of follow-ups in this study. The methods for follow-ups included outpatients visits, contacting by phone, mail, chatting software, or address. The general information of follow-ups included adjuvant therapy, recurrence, the cause of death, et al. The follow-up endpoint (i.e., OS) was defined as the time from operation to death. Patients who were still alive at the cut-off date of follow-ups were censored at the date at which they were last confirmed to be alive. We defined loss to follow up as no-show on the clinical follow-ups or the patients or their family members cannot be contacted by phone, mail, or address.

Analyzed Variables

For all patients, the following demographic and clinicopathological variables were recorded in the database: sex, age, preoperative carbohydrate antigen 19-9 (CA19-9) level, tumor location (head/neck/uncinate, body/tail, or multifocal), intratumoral necrosis, perineural invasion, lymphovascular invasion, R status (R1 or R0), tumor grade (G1/2 or G3), and information on postoperative adjuvant therapy and survival time (i.e., OS). Furthermore, TNM staging was recorded according to the 8th edition of AJCC Cancer Staging Manual for Pancreatic Cancer. With respect to the tumor size, the maximum tumor diameter was reported macroscopically after microscopic corroboration had been used to place the tumors in the correct T-category according to the 8th edition of the AJCC staging system.

Statistical Analysis

Distributional differences in baseline variables between the two cohorts and the association of TSR categories with clinicopathological features were examined using the chi-squared test or Wilcoxon rank-sum test. Variables with $P < 0.05$ in univariate analyses were included in multivariate analyses using logistic regression, and odds ratios (ORs) were calculated. Univariate and multivariate Cox regression analyses were performed to identify independent prognostic factors, and hazard ratios (HRs) were calculated. Variables with $P < 0.1$ in univariate analyses were included in multivariate analyses using a forward selection algorithm. The Kaplan–Meier method and log rank test were used to analyze "time to endpoints." The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the computer-aided method for TSR >1 (high stromal component) were calculated using pathologists' evaluation as the reference. The harmonic mean of recall and precision [F1 score = 2∗Precision∗Recall/(Precision+Recall)] was used to evaluate the accuracy of computer-aided evaluation. Agreement between pathologists' evaluation and computer-aided evaluation was measured using weighted Cohen kappa coefficient (κ). Analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). For all analyses, a two-tailed $P < 0.05$ was considered statistically significant.

TABLE 1 | Baseline characteristics of patients in the developing and validation cohorts.

	Developing cohort	Validation cohort	*P*
Total	207	193	
Age, ≤65/>65 (years)	132/75	125/68	0.835
Sex, male/female	134/73	110/83	0.113
Tumor location, head/neck/uncinate, body/tail, or multifocal	122/75/10	109/79/5	0.365
CA19-9, <37/≥37 U/mL	58/149	45/148	0.282
T stage, T1/2/3	59/122/26	56/119/18	0.582
N stage, N0/1/2	60/99/41	61/96/43	0.456
TNM stage, I/II/III	51/112/44	57/90/46	0.319
Grade, G1/2/3	22/122/63	12/113/68	0.224
TSR, >1/≤1	120/87	112/81	0.849
R status, R0/R1	136/71	120/73	0.463
Postoperative adjuvant therapy, with/without	199/8	187/6	0.681
Median follow-up (months)	14.2	12.4	0.105

CA19-9, carbohydrate antigen 19-9; TNM, tumor–node–metastasis; TSR, tumor–stroma ratio.

RESULTS

Study Population

Of the 440 consecutive patients in our study, 40 were excluded because they had intraoperative metastasis or R2 ($n = 20$), received neoadjuvant chemotherapy or radiotherapy ($n = 4$), had other malignancies in the past ($n = 4$), died within 90 days ($n = 8$), or were lost to follow-up ($n = 4$). All patients enrolled were of yellow race. The developing cohort comprised 207 patients, whereas the validation cohort consisted of 193 patients. In the developing cohort, 87 and 120 patients were deemed to have high and low stromal component, respectively; in the validation cohort, 81 and 112 patients were considered to have high and low stromal component, respectively (**Figure 1**). Relevant baseline variables such as age, sex, tumor location, preoperative CA19-9 level, T stage, N stage, M stage, TNM stage, tumor grade, TSR categories, R status, postoperative adjuvant therapy, and median follow-up period were similarly distributed in the developing and validation cohorts (**Table 1**).

Association Between TSR Categories and Clinicopathological Variables

Representative examples of TSR categories, including high stromal component and low stromal component, are depicted in **Figure 2**. Low stromal component was significantly associated with intratumoral necrosis, G3, and R1 in the developing and validation cohorts ($P < 0.05$; **Table 2**). In logistic regression analyses, two independent variables associated with low stromal

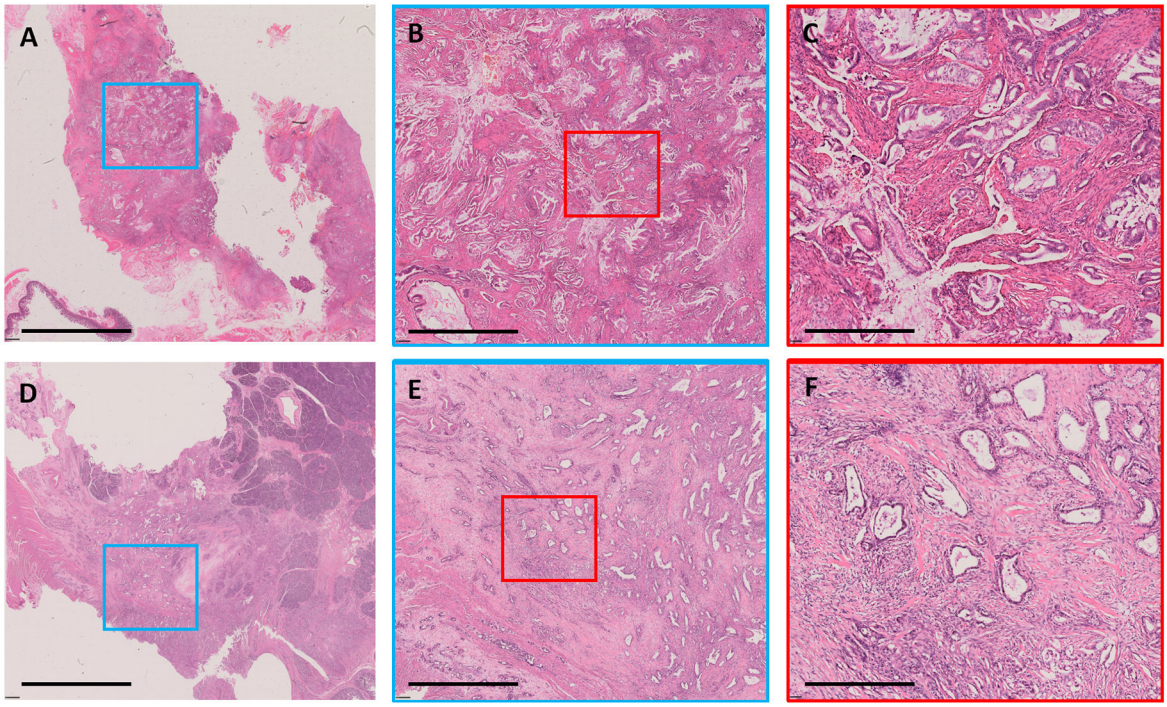

FIGURE 2 | Examples of stromal component. A case with low stromal component shown as whole-mount slide image in **(A)** (3.1×); the blue rectangular box was amplified in **(B)** (12.5×), and the red rectangular box was amplified in **(C)** (50×). A case with high stromal component shown as whole-mount slide image in **(D)** (3.1×); the blue rectangular box was amplified in **(E)** (12.5×), and the red rectangular box was amplified in **(F)** (50×). All images were stained with H&E. The black bar represents 8 mm in **(A,D)**, 2 mm in **(B,E)**, and 0.5 mm in **(C,F)**.

component were identified in the developing cohort—namely, intratumoral necrosis [OR, 3.530; 95% confidence interval (CI), 1.953–6.379; $P < 0.001$] and R1 (OR, 2.281; 95% CI, 1.219–4.265; $P = 0.01$). Both variables were validated in the validation cohort (intratumoral necrosis: OR, 3.890; 95% CI, 2.097–7.217; $P < 0.001$ and R1: OR, 2.034; 95% CI, 1.059–3.910; $P = 0.033$; **Table 3**).

Prognostic Impact of TSR in Cox Regression Analysis

We performed Cox regression analysis to examine the effect of postoperative clinicopathological parameters on prognosis. Univariate analyses revealed that intratumoral necrosis, tumor grade, perineural invasion, T stage, N stage, TNM stage, and stromal component (low vs. high: HR, 2.094; 95% CI, 1.386–3.165; $P < 0.001$) were significantly associated with OS in the developing cohort (**Table 4**). Except for R status (R1 vs. R0: HR, 1.572; 95% CI, 1.062–2.326; $P = 0.024$), the analysis results of the validation cohort were almost similar to those of the developing cohort (**Table 4**). Furthermore, multivariate analysis confirmed that TNM stage (TNM stage II vs. I: HR, 2.584; 95% CI, 1.386–4.819; $P = 0.003$; TNM stage III vs. I: HR, 4.384; 95% CI, 2.285–8.411; $P < 0.001$), stromal component (low vs. high: HR, 1.876; 95% CI, 1.227–2.870; $P = 0.004$), tumor grade (G3 vs. G1/2: HR, 2.124; 95% CI, 1.419–3.179; $P < 0.001$), and perineural invasion (with vs. without: HR, 2.147; 95% CI, 1.187–3.883; $P = 0.011$) were independent prognostic factors in the developing cohort (**Table 5**). The abovementioned independent prognostic factors were also validated in the validation cohort (**Table 5**). Moreover, we found that stromal component categories could classify patients into subgroups and that high stromal component could predict good prognosis within TNM stages I, II, and III, which were also validated in the validation cohort (**Figure 3**).

Agreement Between Pathologists' Evaluation and Computer-Aided Evaluation

To alleviate the pathologists' workload and facilitate standard integration of TSR into routine diagnostics, we compared the evaluation conducted by pathologists and that performed using a computer. Of the 41 patients, 20 were placed by the pathologists in the high stromal component category, whereas 21 were placed in the low stromal component category. In comparison, 18 were placed by the computer in the high stromal component category, whereas 23 were placed in the low stromal component category. After comparing the stromal component categories, the weighted kappa value for categorical assessments between the pathologists' evaluation and computer-aided evaluation was 0.804 (95% CI, 0.573–0.951), suggesting strong agreement (**Table 6**). With pathologists' evaluation as the reference, the sensitivity, specificity, PPV, and NPV for the classification of high stromal component by the computer-aided method were 85, 95.2, 94.4, and 87%, respectively. The precision and recall for the classification of high stromal component by the computer-aided method as compared to pathologists'

TABLE 2 | Association between clinicopathological features and tumor–stroma ratio.

	Developing cohort		*P*	Validation cohort		*P*
	High stromal component (%)	Low stromal component (%)		High stromal component (%)	Low stromal component (%)	
Total	87 (42.0)	120 (58.0)		81 (42.0)	112 (58.0)	
Sex			0.478			0.560
Male	55 (63.2)	70 (58.3)		48 (59.3)	71 (63.4)	
Female	32 (36.8)	50 (41.7)		33 (40.7)	41 (36.6)	
Age (years)			0.504			0.587
≤65	59 (67.8)	76 (63.3)		53 (65.4)	69 (61.6)	
>65	28 (32.2)	44 (36.7)		28 (34.6)	43 (38.4)	
Tumor location			0.835			0.508
Head/neck/uncinate	53 (60.9)	71 (59.2)		41 (50.6)	66 (58.9)	
Body/tail	30 (34.5)	45 (37.5)		37 (45.7)	42 (37.5)	
Multifocal	4 (4.6)	4 (3.3)		3 (3.7)	4 (3.6)	
Intratumoral necrosis			**<0.001**			**<0.001**
Without	58 (66.7)	44 (36.7)		56 (69.1)	42 (37.5)	
With	29 (33.3)	76 (63.3)		25 (30.9)	70 (62.5)	
Grade			**0.004**			**0.011**
1/2	70 (80.5)	74 (61.7)		62 (76.5)	66 (58.9)	
3	17 (19.5)	46 (38.3)		19 (23.5)	46 (41.1)	
Lymphovascular invasion			0.185			0.809
Without	60 (69.0)	72 (60.0)		52 (64.2)	70 (62.5)	
With	27 (31.0)	48 (40.0)		29 (35.8)	42 (37.5)	
Perineural invasion			0.992			0.576
Without	16 (18.4)	22 (18.3)		10 (12.3)	17 (15.2)	
With	71 (81.6)	98 (81.7)		71 (87.7)	95 (84.8)	
T stage			0.234			0.198
1	30 (34.5)	29 (24.2)		29 (35.8)	27 (24.1)	
2	50 (57.5)	77 (64.2)		44 (54.3)	70 (62.5)	
3	7 (8.0)	14 (11.7)		8 (9.9)	15 (13.4)	
N stage			0.700			0.217
0	30 (34.5)	37 (30.8)		28 (34.6)	26 (23.2)	
1	42 (48.3)	57 (47.5)		36 (44.4)	60 (53.6)	
2	15 (17.2)	26 (21.7)		17 (21.0)	26 (23.2)	
TNM stage			0.620			0.199
I	28 (32.2)	33 (27.5)		25 (30.9)	22 (19.6)	
II	43 (49.4)	59 (49.2)		38 (46.9)	62 (55.4)	
III	16 (18.4)	28 (23.3)		18 (22.2)	28 (25.0)	
R status			**0.009**			**0.046**
0	64 (73.6)	67 (55.8)		59 (72.8)	66 (58.9)	
1	23 (26.4)	53 (44.2)		22 (27.2)	46 (41.1)	

TNM, tumor–node–metastasis. The bold value means significant difference (P < 0.05).

evaluation were 94.4 and 85%, respectively. Furthermore, the F1 score was calculated as 89.4%, indicating the high accuracy of the computer-aided method for TSR evaluation as compared to pathologists' evaluation.

DISCUSSION

Based on two representative, well-characterized cohorts of 400 patients with sporadic PDAC, we first showed in our study that the application of the entire tumor scope at 100× for TSR assessment on DWMSIs was a reliable evaluation method for classifying patients with PDAC into subgroups. Because of the intratumoral heterogeneity of PDAC, we evaluated the TSR by assessing the entire tumor scope in order to avoid selecting the most appropriate area for assessment within the tumor. However, the methods that we used might have increased the workload of pathologists, which may hamper its application in routine pathological reporting. Hence, we explored the computerized model to offset the shortcoming. The results of computerized evaluation for TSR,

TABLE 3 | Clinicopathological features associated with low stromal component according to multivariate logistic regression analysis.

	Developing cohort		Validation cohort	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Intratumoral necrosis, with vs. without	3.530 (1.953–6.379)	**<0.001**	3.890 (2.097–7.217)	**<0.001**
R status, R1 vs. R0	2.281 (1.219–4.265)	**0.01**	2.034 (1.059–3.910)	**0.033**

CI, confidence interval; OR, odds ratio. The bold value means significant difference (P < 0.05).

TABLE 4 | Univariate Cox regression analyses of clinicopathological features associated with OS of patients with PDAC.

	Developing cohort		Validation cohort	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Intratumoral necrosis, with vs. without	2.021 (1.379–2.962)	**<0.001**	1.616 (1.087–2.402)	**0.018**
Grade, G3 vs. G1/2	2.303 (1.557–3.405)	**<0.001**	2.156 (1.449–3.209)	**<0.001**
Lymphovascular invasion, with vs. without	1.235 (0.842–1.811)	0.280	1.170 (0.788–1.736)	0.437
Perineural invasion, with vs. without	2.378 (1.328–4.258)	**0.004**	3.020 (1.401–6.512)	**0.005**
T stage		**0.010**		**0.022**
T2 vs. T1	1.191 (0.761–1.864)	0.443	1.510 (0.948–2.405)	0.083
T3 vs. T1	2.373 (1.322–4.262)	**0.004**	2.509 (1.300–4.841)	**0.006**
N stage		**<0.001**		**<0.001**
N1 vs. N0	1.812 (1.062–3.090)	**0.029**	1.997 (1.186–3.365)	**0.009**
N2 vs. N0	3.662 (2.082–6.439)	**<0.001**	3.915 (2.292–6.686)	**<0.001**
TNM stage		**<0.001**		**<0.001**
Stage II vs. stage I	2.641 (1.403–4.869)	**0.002**	2.545 (1.436–4.512)	**0.001**
Stage III vs. stage I	5.053 (2.643–9.660)	**<0.001**	4.707 (2.642–8.388)	**<0.001**
Stroma, low stromal component vs. high stromal component	2.094 (1.386–3.165)	**<0.001**	2.390 (1.574–3.629)	**<0.001**
R status, R1 vs. R0	1.377 (0.936–2.028)	0.105	1.572 (1.062–2.326)	**0.024**

Postoperative adjuvant therapy was not added as a variable here, because nearly all patients were treated.
CI, confidence interval; OR, odds ratio; TNM, tumor–node–metastasis. The bold value means significant difference (P < 0.05).

were highly consistent with those of pathologists' evaluation. This considerably simplifies TSR assessment and can facilitate the standard integration of TSR into routine diagnostics, promoting its regular inclusion in histopathology reports and helping in the more accurate prognostic classification of patients with PDAC. Nevertheless, there is still uncertainty about whether or not immunohistochemistry, which can distinguish activated stroma (22), should be used. Although a previous study showed that the increased α-smooth muscle antigen positive stromal component of tumor indicated the reduced survival time of patients with PDAC (23), fibroblast activation protein-α has recently rose to prominence as a marker that defines a more pro-tumorigenic stromal component (24). Thus, activated stroma evaluation may be more complicated and unreliable; in addition, the immunohistochemistry technique is more complex, expensive, and irreproducible than H&E staining and is difficult to apply in the routine pathological reporting system. Based on the above analyses, the pathological technique for TSR evaluation that we employed is fairly exact, simple, cost-effective, and reproducible to be used for classifying patients with PDAC into subgroups.

We used the optimized evaluation method to assess TSR and found that G3 was closely related to the low stromal component of the tumor, which is consistent with the finding of a previous study wherein a high degree of desmoplasia was inversely correlated to differentiated tumor grade in genetically engineered mice (22). The results of our study indicated that intratumoral necrosis and R1 were independently associated with low stromal component. Interestingly, treatment with halofuginone, which altered the immune landscape in PDAC by decreasing the stromal component, with greater immune infiltrate into low-hyaluronan regions, was reported to result in an increased number and distribution of both classically activated inflammatory macrophages and cytotoxic T cells. In concert with a direct effect on carcinoma cells, this led to widespread intratumoral necrosis (25). Hence, low stromal component and weakened stromal barriers in tumors may facilitate the infiltration of inflammatory and immune cells, which may directly participate in the formation of intratumoral necrosis. In another study, neoadjuvant treatment resulted in tumor cell death, with the remaining tumor cells lying at a greater distance from each other, which was closely related to a low R1 rate (26). This may indicate that PDAC with low stromal component is more likely to have an R1 status in pathological reports. Whereas, the result may be related with a surgical bias. Probably tumors with high stromal component are characteristic by hardness, so the surgeons tended to resect more pancreatic tissue to achieve a

TABLE 5 | Multivariate Cox regression analyses of clinicopathological features associated with OS of patients with PDAC.

	Developing cohort		Validation cohort	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
TNM stage		**<0.001**		**<0.001**
Stage II vs. stage I	2.584 (1.386–4.819)	**0.003**	2.122 (1.186–3.794)	**0.011**
Stage III vs. stage I	4.384 (2.285–8.411)	**<0.001**	4.443 (2.042–6.625)	**<0.001**
Stroma Low stromal component vs. high stromal component	1.876 (1.227–2.870)	**0.004**	2.047 (1.322–3.168)	**0.001**
Grade G3 vs. G1/2	2.124 (1.419–3.179)	**<0.001**	1.751 (1.158–2.649)	**0.008**
Perineural invasion With vs. without	2.147 (1.187–3.883)	**0.011**	2.351 (1.080–5.119)	**0.031**

CI, confidence interval; HR, hazard ratio; TNM, tumor–node–metastasis. The bold value means significant difference (P < 0.05).

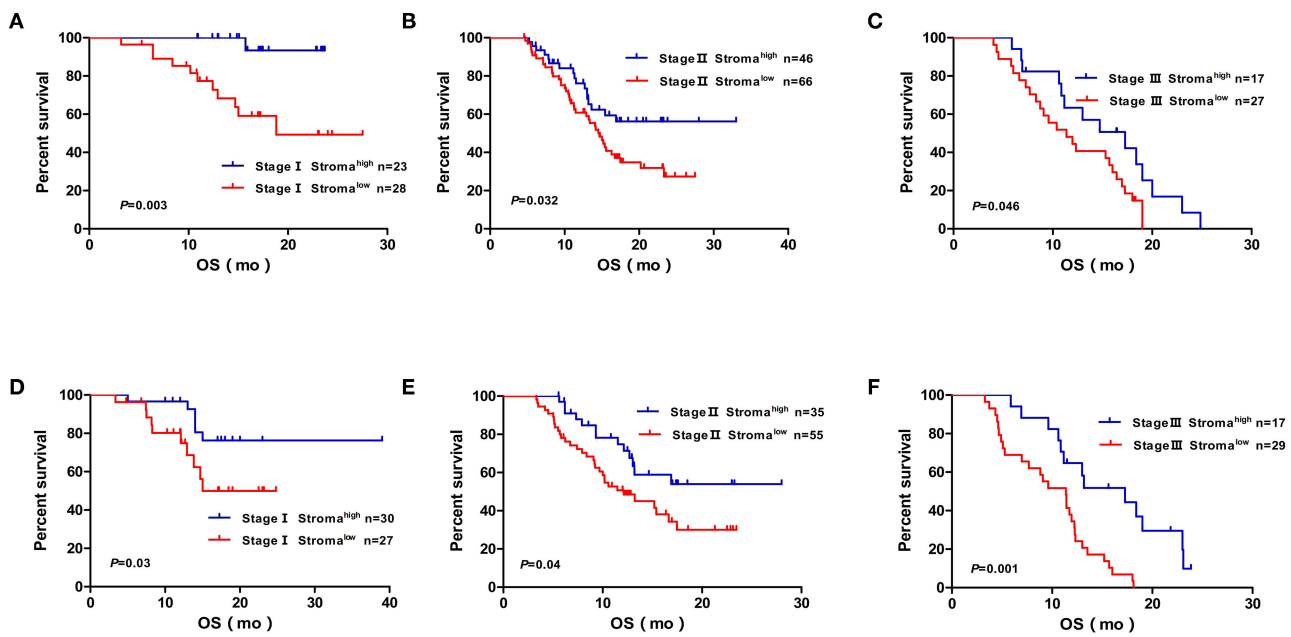

FIGURE 3 | Kaplan–Meier diagrams showing OS for TSR subgroups based on the TNM stage in the developing cohort **(A,B,C)** and validation cohort **(D,E,F)**. *P*-values for log rank test are shown in each panel. OS, over survival; mo, months.

negative margin. However, no consensus has been reached on the prognostic impact of stromal component in patients with PDAC based on previous studies (7–9).

We also found that TSR categories could be a strong and independent prognostic factor in patients with PDAC and demonstrated that the prognostic impact of TSR was almost similar with tumor grade and perineural invasion, which are regularly included in pathological reports. Thus, the TSR would considerably improve the prognostic stratification of patients with PDAC, considering the simplified and reliable assessment methods. In our study, TSR categories could successfully stratify patients according to TNM stages I, II, and III in both the developing and validation cohorts. This may be profoundly significant to manage postoperative therapy. In addition to embracing newer strategies comprising genomics, stromal therapies, and immunotherapies, conventional approaches using chemotherapy and radiotherapy still offer considerable prospects for greater traction and synergy with evolving concepts (27). Moreover, chemotherapy resistance may be closely related to stromal component (28, 29). Stroma features that improve risk assessment have the potential to facilitate treatment, leading to a more efficient management of this patient population. Considering that recent studies have shown no molecular differences between very long-term and short-term survivors among patients with PDAC (30) and that pathological prognostic markers, such as the TSR, could aid in identifying high-risk groups, TSR assessment in PDAC would be an additional factor to help select patients who would benefit from a more intensified chemotherapy approach. Thus, validated prognostic factors, including the TSR, can substantially increase the probability

TABLE 6 | Agreement between pathologists' evaluation and computer-aided evaluation and the weighted kappa value.

		Pathologists' evaluation		Kappa (95% CI)
		High stromal component	Low stromal component	
Computer-aided evaluation	High stromal component	17	1	0.804 (0.573–0.951)
	Low stromal component	3	20	

CI, confidence interval.

of a more individualized therapy and may even be added to the stage classification of tumors for better identification of patient subgroups and, consequently, for a more personalized management of patients with PDAC.

TSR assessment can be performed not only using pathology but also using radiology. Previous studies reported that the stromal component evaluated using radiology exhibited good correlation with that evaluated using pathology and high stromal component was associated with a relatively long survival time (15, 31), which coincide with the results of our research. This may be explained by the advantages of the assessment of the entire tumor, which links microscopic pathology to macroscopic radiology. More importantly, TSR calculation using radiology can predict the prognosis of metastatic tumors and may guide the management of patients undergoing neoadjuvant therapy who cannot undergo upfront surgery. In a subsequent research, we will attempt to clarify the relationship between the TSR evaluated using radiology and the prognosis of patients with PDAC, which may make TSR evaluation independent from the specimens obtained postoperatively.

The present study has several limitations. First, our study has the intrinsic shortcomings of any retrospective study. Second, the specific pathological methods for the TSR assessment used in this study made it difficult to perform external validation. We have been studying to identify the representative part of the whole tumor specimen for TSR evaluation, so that the assessment method will be pervasively applicable and external validation can be easily conducted in the future. Third, a small number of patients were evaluated using the computer-aided method.

CONCLUSION

Our findings indicate that TSR evaluation in PDAC according to the assessment method that we first used and validated provides independent prognostic information complementary to the TNM staging system. Moreover, we demonstrate the robustness and potential of a simple, standardized, inexpensive, and reliable scoring system, which may facilitate routine TSR documentation in histopathology reports of patients with PDAC.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Changhai Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BoL, SGu, and GJ: study idea and design. BoL, YW, HJ, BaL, XS, SGa, ZZ, and CN: acquisition, analysis, or interpretation of the data. BoL, YW, and HJ: initial drafts. SGu, JX, and GJ: critical revision for important intellectual content. All authors approved the final version of the manuscript and are accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.01472/full#supplementary-material

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A Novel Nomogram to Predict Survival in Patients With Recurrence of Pancreatic Ductal Adenocarcinoma After Radical Resection

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The post-progression survival (PPS) of patients with pancreatic ductal adenocarcinoma (PDAC) after radical resection is varied and influenced by the characteristics of tumor progression. We aimed to establish and validate a nomogram to predict PPS for PDAC patients after surgery. A total of 302 PDAC patients who had undergone curative resection from 2008 to 2018 were enrolled in this study and randomly divided into training and validation cohorts at a ratio of 3:1. The nomogram was established based on independent prognostic factors selected by LASSO and Cox regression and measured by the area under the receiver operating characteristic curve (AUC) and the concordance index (C-index). Significant prognostic factors included carbohydrate antigen 19-9 (CA19-9), lymph node (LN)9 metastasis, LN14 metastasis, LN16 metastasis, tumor differentiation, imaging-detected tumor size, local progression, liver-only metastasis, lung-only metastasis, and multiple metastases. The nomogram built on these factors showed powerful efficacy in PPS prediction, with C-index values of 0.751 (95% CI 0.692–0.0.810) and 0.710 (95% CI 0.645–0.755) for the training and validation cohorts, respectively. The AUC values for the 1-year and 2-year PSS rates were 0.745, 0.747, and 0.783, 0.748, respectively; these values were higher than those of the 8th tumor–node–metastasis (TNM) stage system. The exploration of risk factors and the establishment of a nomogram can provide new versions of personalized recurrence management for PDAC patients after surgery.

Keywords: pancreatic ductal adenocarcinoma, recurrence, surgery, nomogram, prognosis

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with a 5-year overall survival (OS) rate of only 7% (1). Despite its low incidence, cancer-related deaths of PDAC patients rank fourth in the United States and continue to increase; thus, PDAC is expected to become the second-most common cause of cancer-related death by 2030 (2). Surgical resection, the only way of obtaining curative treatment of PDAC, is suitable for less than 20% of patients and improves the 5-year OS rate to 20–30% (3). Moreover, up to 80% of PDAC patients suffer recurrence soon after curative

resection (4). Therefore, early recurrence poses a major challenge for the long-term survival of PDAC patients after curative resection.

Several stage systems have been used to estimate the OS or progression-free survival of PDAC patients (5, 6). These instruments were constructed on the basis of variables limited to primary tumor features. However, PDAC patients with varied progression patterns may have different rates of post-progression survival (PPS), which is greatly impacted by features of progression rather than primary tumor features (4, 7). Therefore, previously developed predictive systems may be less effective for PPS estimation in PDAC patients after surgery. Considering the absence of a predictive model specifically designed for PPS estimation, it was necessary to build a clinical prognostic predictive system to estimate PPS as well as recurrence after surgery in individual PDAC patients.

In the present study, we established a prognostic nomogram to predict the PPS of PDAC patients after curative resection. We also conducted comparisons of the efficacy of predicting survival prediction between this nomogram and a tumor–node–metastasis (TNM) system.

MATERIALS AND METHODS

Patients

Consecutive PDAC patients who had undergone radical resection from 2008 to 2018 at Sun Yat-sen University Cancer Center (SYSUCC) were included in this study. The exclusion criteria were as follows: (1) distant metastasis before surgery, (2) history of a second tumor, (3) follow-up period $<$ 1 year, (4) missing information from follow-up records, and (5) microscopic or macroscopic incomplete resection. The margin for radical resection was defined as 1.5–2 mm, as in previous studies (8, 9). This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. All procedures involving human participants in the present study were performed in accordance with the ethical standards of institutional and/or national research committees as well as the 1964 Helsinki Declaration and its later amendments or similar ethical standards. Written informed consent was obtained from the patients prior to treatment.

Data Collection

Resectability was judged by a pancreatic multidisciplinary team based on radiological examination, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/CT (PET-CT). Specialized pancreatic surgeons performed all radical resections of PDAC. An experienced pancreatic pathologist carried out the pathological diagnosis and description of the specimens, including such characteristics as tumor size, tumor differentiation, lymph node (LN) metastasis, LN total number, LN positive number, satellite foci, macrovascular and microvascular invasion, lymph vessels, and perineural and adjacent organ invasion. LN ratio (LNR) was defined as the proportion of positive LN in the total examined LN. Additionally, the associated radiological and clinical variables described in our previous studies (7) were included in the present study. All blood test indexes were obtained at the time at which tumor progression was diagnosed. Previously described (10) inflammation-based indexes, including the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the modified Glasgow Prognostic Score (mGPS), the prognostic nutritional index (PNI), the prognostic index (PI), and the systemic immune-inflammation index (SII), were analyzed as well.

Recurrence Patterns

Information regarding the timing and pattern of recurrence was obtained at regular follow-up, which consisted of regular chest and abdominal CT, carbohydrate antigen 19-9 (CA19-9) measurement, and carcinoembryonic antigen (CEA) measurement every 3 months after surgery. Additional imaging modalities, such as MRI and PET/CT, were selectively performed to determine patterns of recurrence. When imaging findings were consistent with recurrence, biopsy was rarely performed. Otherwise, biopsy was conducted to confirm tumor progression or metastases. Either radiological or histological evidence was required for the diagnosis of disease recurrence. The date of the last follow-up occurred at the end of May 2019. The first location of recurrence was used to describe the recurrence patterns, which were categorized as in the study by Groot et al. (4). The cutoff value differentiating early and late progression was defined as 1 year following surgery (11). The terms liver-only and lung-only metastases referred to isolated hepatic and lung recurrence, respectively. The term others referred to isolated recurrence in other less common areas. Local recurrence and isolated distant metastasis occurring simultaneously were classified as local + distant while the term multiple referred to multiple distant metastases.

Survival Outcomes and Statistical Analysis

Tumor progressions occurring within and beyond 1 year following surgery were classified as early and late progressions, respectively. Comparisons between the early and late progression groups were conducted for various clinical and pathological variables using chi-square analysis. The main survival outcome of this study was PPS, which was defined as the duration from the date of tumor progression to the date of death or the last date of follow-up. The Kaplan–Meier method was used to estimate survival. When the survival curves were not crossed, the survival differences were compared using a log-rank test. When the survival curves were crossed, the survival differences were further analyzed by landmark analysis. Multivariate analysis was adopted to determine significant prognosis factors based on the results of univariate analysis and the least absolute shrinkage and selection operator (LASSO) logistic regression model, which was used to explore the relationships between pathological and radiological variables and PPS. The area under the receiver operating characteristic (ROC) curves (AUCs) and concordance indexes (C-indexes) of the multimarker algorithms were calculated and compared with those of the TNM stage system. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were conducted

using SPSS software version 22 (SPSS Inc., Chicago, IL, USA) and R software version 3.6.1 (R Development Core Team; http://www.r-project.org).

RESULTS

Patients

A total of 355 PDAC patients had received radical resection from 2008 to 2018 at SYSUCC. Fifty-three patients were excluded from this study according to the exclusion criteria, including microscopic or macroscopic incomplete resection (10 patients), history of a second tumor (12 patients), and missing information from follow-up records (31 patients). Ultimately, 302 patients were included in the present study. Each patient was followed up for more than 1 year and the median follow-up time was 24.7 months [95% confidence interval (CI) 20.3–29.1 months]. During the follow-up period, a total of 173 (57.3%) patients developed tumor progressions after surgery. Comparisons between the early and late progression groups for clinical, pathological, and radiological variables are shown in **Table 1**. All patients were randomly divided into training (n = 227) and validation (n = 75) cohorts in a 3:1 ratio for the establishment and validation of the nomogram.

COMPARISONS OF CHARACTERISTICS BETWEEN EARLY AND LATE PROGRESSION GROUPS

Apart from 129 patients who were free of tumor progression, 129 and 44 patients were included in the early and late tumor progression groups, respectively. As shown in **Table 1**, the distribution of clinical factors including age, gender, and inflammation-based indexes, was balanced between these three groups, while higher CA19-9 and CEA levels were positively associated with early tumor progression. In terms of pathological factors, patients in the early progression group were more likely to have LN metastases as well as large and poorly differentiated tumors. Significantly large proportions of patients in the early progression group had LN16 metastases, imaging-detected vascular invasion, and more advanced stages of TNM. Additionally, compared with patients in the late progression group, those in the early progression group were more likely to have liver metastases and local recurrence.

Comparisons of PPS Stratified by Different Progression Patterns

Overall, there were six different types of tumor progressions for PDAC patients after surgery. Liver-only metastasis was the most common progression type, followed by local recurrence, local and distant progression, and lung-only metastasis. Metastases at other sites and multiple metastases occupied a small proportion of tumor progressions. The median PPS for all patients was 13.53 months (95% CI 11.24–15.83), and the 1-, 2-, and 3-year PPS rates were 55.9, 26.4, and 10.7%, respectively. Patients with different progression patterns had varied survival rates. As shown in **Figure 1**, patients with local recurrence had the longest median PPS of 15.93 months (95% CI 11.07–25.03), followed by patients with lung-only metastasis (median PPS 14.7 months, 95% CI 14.00–30.43) and liver-only metastasis (median PPS 12.6 months, 95% CI 9.83–15.77). Landmark analysis was used to analyze survival differences when the survival curves were crossed. The comparisons of survival rates between local recurrence and other sites, between liver-only metastasis and multiple metastases, and between lung-only metastasis and multiple metastases revealed that the former had significantly higher survival rates ($P <$ 0.05) than the latter at 1 year following tumor progression (the landmark point for the survival analyses). Further, patients with local progression had significantly higher survival rates than those with multiple analyses, while survival rates were similar between the other comparison groups. Overall, multiple metastases corresponded with the poorest survival rates among these progression patterns.

Prognostic Factors for PPS

In order to investigate prognostic factors for PPS, a LASSO-penalized Cox regression analysis was performed based on 48 high-dimensional radiological and pathological data to further reduce the number of factors in the selected panel with the best predictive performance using the 10-fold cross-validation (**Figure 2**). Nine variables were selected for PPS prediction by the LASSO-Cox regression model, including LN9 metastasis, LN14 metastasis, LN16 metastasis, local recurrence, liver metastasis, lung metastasis, multiple metastases, tumor differentiation, and imaging-detected tumor size. These predictors, alone with the associated clinical variables identified by univariate analysis, were incorporated in the multivariate analysis. Independent prognostic factors for PPS in PDAC patients following surgery included CA19-9 (HR = 2.524, 95% CI 1.002–6.359, P = 0.050), LN9 metastasis (HR = 1.351, 95% CI 1.092–3.430, P = 0.042), LN14 metastasis (HR = 1.304, 95% CI 1.074–1.944, P = 0.042), LN16 metastasis (HR = 2.785, 95% CI 1.736–10.534, P = 0.031), tumor differentiation (HR = 0.492, 95% CI 0.248–0.974, P = 0.042), imaging-detected tumor size (HR = 1.579, 95% CI 1.187–2.371, P = 0.043), local progression (HR = 5.952, 95% CI 1.869–18.868, P = 0.003), liver-only metastasis (HR = 6.452, 95% CI 1.919–21.739, P = 0.003), lung-only metastasis (HR = 4.405, 95% CI 1.869–18.868, P = 0.046), and multiple metastases (HR = 3.578, 95% CI 1.147–15.887, P = 0.042) (**Table 2**).

Construction and Validation of Nomogram for PPS Prediction

As shown in **Figure 3**, a specific nomogram was built based on independent prognostic factors for PPS. LN16 metastasis demonstrated the most prominent effect in PPS prediction, followed by local recurrence and liver-only metastasis. Calibration plots showed high agreement between predicted and actual survival in both training and validation cohorts (**Figure 4**). The C-indexes of the nomogram based on the training and validation cohorts were 0.751 (95% CI 0.692–0.0.810) and 0.710 (95% CI 0.645–0.755), respectively; these values were significantly higher than those of the 8th TNM stage system (**Table 3**). Comparisons of discriminatory capacity between the nomogram and the 8th TNM stage system were

TABLE 1 | Clinicopathological characteristics of patients with PDAC.

Characteristics		Time to progression					Characteristics		Time to progression				
		Absence	Early progression	Late progression	*N*	*P*			Absence	Early progression	Late progression	*N*	*P*
Whole cohort		129	129	44	302		Macrovascular invasion	Absence	120	114	39	273	0.408
Age	≤60 years	74	70	20	164	0.391		Presence	9	15	5	29	
	>60 years	55	59	24	138		Microvascular invasion	Absence	87	85	34	206	0.364
Gender	Male	53	46	20	119	0.453		Presence	42	44	10	96	
	Female	76	83	24	183		Lymph vessel invasion	Absence	65	55	20	140	0.199
Recurrence	Absence	129	24	21	174	<0.001		Presence	62	76	74	162	
	Presence	0	105	23	128		Perineural invasion	Absence	70	55	21	146	0.174
TNM stage	IA	33	10	11	54	0.001		Presence	59	74	23	156	
	IB	36	25	13	74		Adjacent organ invasion	Absence	119	112	39	270	0.361
	IIA	11	20	4	35			Presence	10	17	5	32	
	IIB	32	38	9	79		LNR	0	83	61	29	173	0.036
	III	17	36	7	60			0–0.16	26	32	8	66	
Recurrence patterns	Absence	129	24	21	174	<0.001		>0.16	20	36	7	63	
	Local	0	29	10	39		Satellite foci	Absence	123	120	44	287	0.180
	Liver-only	0	43	6	49			Presence	6	9	0	15	
	Lung-only	0	10	2	12		Pancreatic membrane invasion	Absence	81	74	28	183	0.608
	Other sites	0	1	4	5			Presence	48	55	16	119	
	Local + distant	0	13	1	14		PI	0	93	78	28	199	0.310
	Multiple	0	9	0	9			1	31	40	13	84	
LN metastasis	Absence	83	61	30	174	0.007		2	5	11	3	19	
	Presence	46	68	14	128		Imaging tumor size (cm)	≤2	63	30	11	104	<0.001
LN5 metastasis	Absence	127	129	44	300			2–4	45	68	28	141	
	Presence	2	0	0	2			>4	21	31	5	57	
LN6 metastasis	Absence	126	128	44	298	0.391	Imaging LN metastasis	Absence	73	75	27	175	0.856
	Presence	3	1	0	4			Presence	56	54	17	127	
LN7 metastasis	Absence	128	126	42	296	0.283	Imaging vascular invasion	Absence	106	90	38	234	0.018
	Presence	1	3	2	6			Presence	23	39	6	68	

(Continued)

TABLE 1 | Continued

Characteristics		Time to progression					Characteristics		Time to progression				
		Absence	Early progression	Late progression	*N*	*P*			Absence	Early progression	Late progression	*N*	*P*
LN8 metastasis	Absence	126	126	42	294	0.698	Imaging LN size (cm)	≤0.5	72	76	29	177	0.715
	Presence	3	3	2	8			0.5–1	30	28	6	64	
LN9 metastasis	Absence	125	125	42	292	0.885		>1	27	25	9	61	
	Presence	4	4	2	10		NLR	≤3.32	89	79	29	197	0.423
LN10 metastasis	Absence	127	125	43	295	0.710		>3.32	40	50	15	105	
	Presence	2	4	1	7		dNLR	≤3.32	39	42	19	100	0.284
LN11 metastasis	Absence	126	124	44	294	0.367		>3.32	90	87	25	202	
	Presence	3	5	0	8		PLR	≤98.13	17	13	6	36	0.692
LN12 metastasis	Absence	116	111	41	268	0.370		>98.13	112	116	38	266	
	Presence	13	18	3	34		PNI	0	31	26	8	65	0.633
LN13 metastasis	Absence	103	92	36	231	0.181		1	98	103	36	237	
	Presence	26	37	8	71		SII	≤1000	90	86	30	206	0.867
LN14 metastasis	Absence	122	117	42	281	0.375		>1000	39	43	14	96	
	Presence	7	12	2	21		mGPS	0	93	81	28	202	0.558
LN15 metastasis	Absence	127	123	44	294	0.367		1	23	33	11	67	
	Presence	2	6	0	8			2	13	15	5	33	
LN16 metastasis	Absence	127	113	44	284	<0.001	WBC	≤10	124	115	41	280	0.097
	Presence	2	16	0	18			>10	5	14	3	22	
LN17 metastasis	Absence	124	125	44	293	0.424	ALB (g/L)	≤35	19	21	6	46	0.895
	Presence	5	4	0	9			>35	110	108	38	256	
LN18 metastasis	Absence	126	126	44	296	0.593	CRP (ng/L)	≤3	93	81	28	202	0.251
	Presence	3	3	0	6			>3	36	48	16	100	
Positive LN number	0	83	61	29	173	0.016	CA19-9 (U/ml)	≤35	34	16	9	59	0.018
	1–3	36	46	13	95			>35	95	113	35	243	
	>4	10	22	2	34		CEA (ng/ml)	≤5	97	77	31	205	0.026
Tumor size (cm)	≤2	48	24	16	88	0.007		>5	32	52	13	97	
	2–4	60	68	18	146		HBV infection	Absence	120	122	41	283	0.866
	>4	21	37	10	68			Presence	9	7	3	19	
Tumor differentiation	Well	0	2	0	2	0.009	Chemotherapy	No	78	58	24	160	0.043
	Moderate	72	55	26	153			Yes	51	71	20	142	
	Poor	57	72	18	147								

M, month; LN, lymph node metastasis; LNR, lymph node ratio; TNM, tumor–node–metastasis stage; PI, prognostic index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; mGPS, modified Glasgow Prognostic Score; WBC, white blood cell count; ALB, albumin; CRP, C-reactive protein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; HBV, hepatitis B virus.

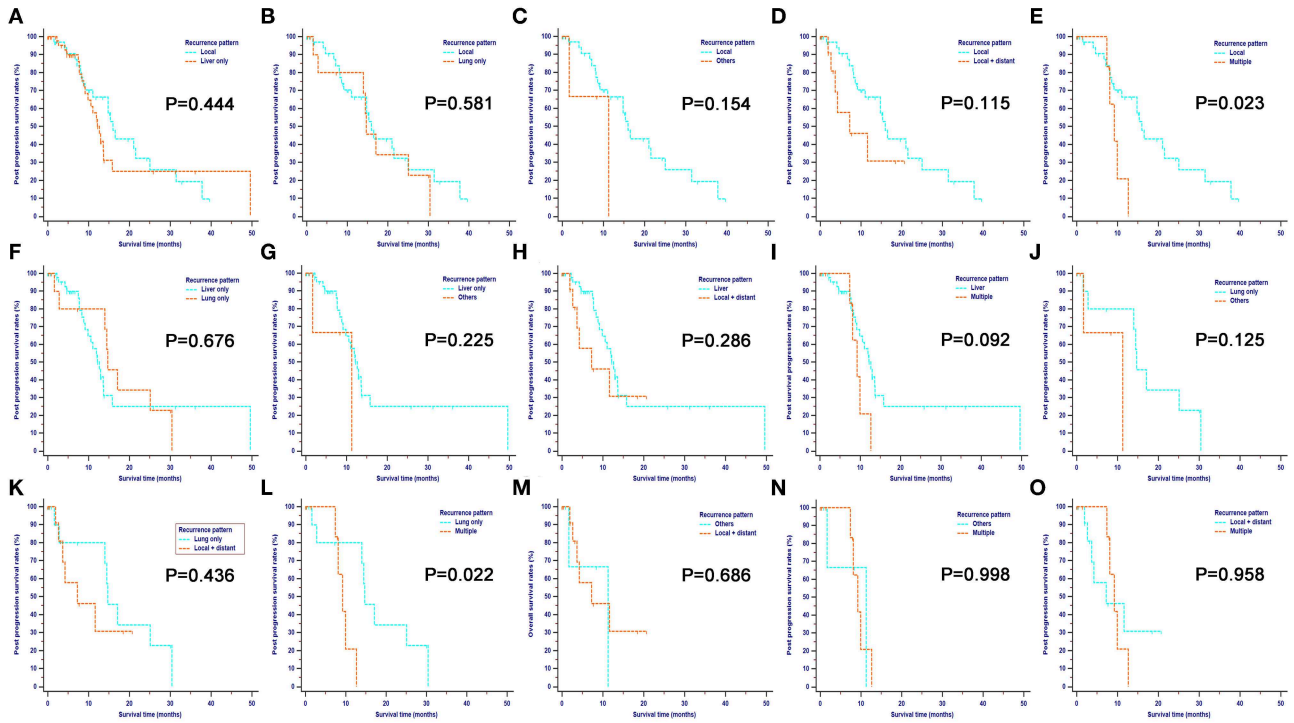

FIGURE 1 | Pairwise comparison of post-progression survival for different tumor progression patterns. Stratification of patients by comparing the following patterns of progression: local vs. liver only **(A)**; local vs. lung only **(B)**; local vs. others **(C)**; local vs. local + distant **(D)**; local vs. multiple **(E)**; liver only vs. lung only **(F)**; liver only vs. others **(G)**; liver only vs. local + distant **(H)**; liver only vs. multiple **(I)**; lung only vs. others **(J)**; lung only vs. local + distant **(K)**; lung only vs. multiple **(L)**; others vs. local + distant **(M)**; others vs. multiple **(N)** and local + distant vs. multiple **(O)**. Landmark analysis was used to analyze survival differences whose survival curves were crossed. For the comparisons of survival rates between local recurrence and other sites, liver-only metastasis and multiple metastases, lung-only metastasis, and multiple metastases, the former had significantly higher survival rates ($P < 0.05$), compared with the latter after 1 year since tumor progression, which was used as the landmark point for survival analyses. Also, patients with local progression had significantly higher survival rates compared with those with multiple analyses while survival rates were similar between other comparison groups. Overall, multiple metastases contributed to the poorest survival among these progression patterns.

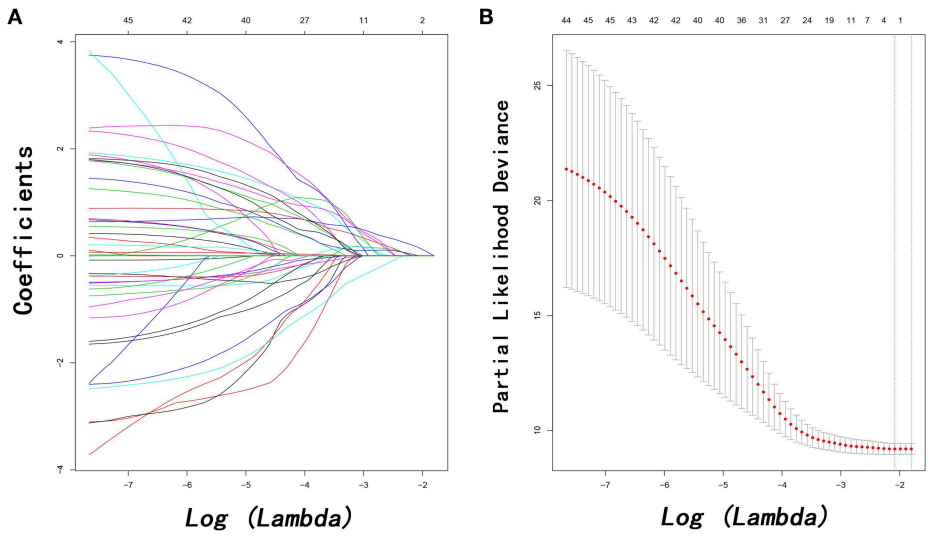

FIGURE 2 | Feature selection using the least absolute shrinkage and selection operator (LASSO) Cox regression model. LASSO coefficient profiles of 48 variables against the log (Lambda) sequence for PPS **(A)** and tuning parameter (Lambda) selection in the LASSO model used 10-fold cross-validation via minimum criteria for PPS **(B)**. PPS, post-progression survival.

TABLE 2 | Independent prognostic factors for PPS.

Characteristics	Levels		PPS					
			Univariate analysis			Multivariate analysis		
			HR	95% CI	*P*	HR	95% CI	*P*
Age	≤60 years	123	Reference		0.819			NI
	>60 years	104	0.942	0.563–1.576				
Gender	Male	90	Reference		0.088			NI
	Female	137	0.640	0.384–1.068				
WBC	≤10	210	Reference		0.010	Reference		0.054
	>10	17	2.488	1.242–4.983		6.125	0.967–38.805	
NLR	≤3.32	62	Reference		0.527			NI
	>3.32	165	1.193	0.690–2.063				
dNLR	≤3.32	76	Reference		0.215			NI
	>3.32	151	1.399	0.823–2.380				
PLR	≤98.13	27	Reference		0.307			NI
	>98.13	200	0.676	0.319–1.434				
PNI	0	49	Reference		0.481			NI
	1	178	1.277	0.647–2.522				
SII	≤1000	155	Reference		0.173			NI
	>1000	72	1.505	0.836–2.709				
mGPS	0	152	Reference					NI
	1	50	1.072	0.501–2.296	0.857			
	2	25	1.198	0.494–2.909	0.689			
PI	0	149	Reference			Reference		
	1	64	0.435	0.201–0.944	0.035	3.090	0.424–22.525	0.266
	2	14	0.384	0.161–0.920	0.032	2.863	0.447–18.341	0.267
ALB (g/L)	≤35	35	Reference		0.815			NI
	>35	192	1.085	0.549–2.143				
CRP (ng/L)	≤3	152	Reference		0.887			NI
	>3	75	1.039	0.612–1.762				
CA19-9 (U/ml)	≤35	44	Reference		0.009	Reference		0.050
	>35	183	2.719	1.279–5.780		2.524	1.002–6.359	
CEA (ng/ml)	≤5	154	Reference		0.941			NI
	>5	73	0.980	0.581–1.654				
HBV infection	Absence	213	Reference		0.445			NI
	Presence	14	1.577	0.490–5.080				
Chemotherapy	No	120	Reference		0.584			NI
	Yes	107	1.165	0.675–2.010				
Time period to recurrence (month)	>24	14	Reference					NI
	≤6	54	4.085	0.864–19.308	0.076			
	6–12	43	3.244	0.766–13.748	0.110			
	12–24	20	2.405	0.569–10.171	0.233			
LN9 metastasis	Absence	219				Reference		0.042
	Presence	8				1.351	1.092–3.430	
LN14 metastasis	Absence	211				Reference		0.038
	Presence	16				1.304	1.074–1.944	
LN16 metastasis	Absence	213				Reference		0.031
	Presence	14				2.785	1.736–10.534	
Tumor differentiation	Well	2				Reference		
	Moderate	115				0.569	0.051–6.305	0.646
	Poor	110				0.492	0.248–0.974	0.042

(Continued)

TABLE 2 | Continued

Characteristics	Levels		PPS					
			Univariate analysis			Multivariate analysis		
			HR	95% CI	*P*	HR	95% CI	*P*
Pathological tumor size (cm)	≤2	66				Reference		
	2–4	110				2.058	0.608–6.960	0.246
	>4	51				1.097	0.370–3.251	0.867
Imaging tumor size (cm)	≤2	78				Reference		
	2–4	106				1.579	1.187–2.371	0.043
	>4	43				0.840	0.461–1.531	0.569
Local progression	Absence	30				Reference		0.003
	Presence	197				5.952	1.869–18.868	
Liver-only metastasis	Absence	37				Reference		0.003
	Presence	190				6.452	1.919–21.739	
Lung–only metastasis	Absence	9				Reference		0.046
	Presence	218				4.405	1.869–18.868	
Other metastases	Absence	4				Reference		0.583
	Presence	223				0.590	0.090–3.872	
Local + distant metastasis	Absence	11				Reference		0.377
	Presence	216				0.516	0.119–2.240	
Multiple metastases	Absence	7				Reference		0.042
	Presence	220				3.578	1.147–15.887	
Microvascular invasion	Absence	155				Reference		0.533
	Presence	72				1.237	0.634–2.416	
Imaging vascular invasion	Absence	176				Reference		0.255
	Presence	51				0.519	0.195–1.542	
Imaging LN size (cm)	≤0.5	133				Reference		
	0.5–1	48				0.566	0.258–1.242	0.156
	>1	46				0.914	0.360–2.325	0.851
LNR	0	130				Reference		
	0–0.16	50				0.502	0.223–1.130	0.096
	>0.16	47				0.447	0.185–1.080	0.074

PPS, post-progression survival; HR, hazard ratio; CI, confidence interval; NI, not include; other abbreviations as in ***Table 1****.*

conducted using ROC curves (**Figure 5**). For the training and validation cohorts, the AUC values for 1-year and 2-year PSS rates were 0.745, 0.747, and 0.783, 0.748, respectively; these values were also higher than those of the 8th TNM stage system (**Figure 5**).

DISCUSSION

Recurrence is an important feature of PDAC after surgery, as it contributes to poor prognosis (7). Previous studies have shown that more than 60% of PDAC patients develop tumor recurrence (12). Similar results were also obtained in the present study, in that the patients in this study experienced a recurrence rate of 57.3%. Given that the survival time of PDAC patients decreases significantly after tumor progression, it is necessary to establish an efficient prognostic system to predict PPS in these patients. Using a large cohort, we developed and validated a novel nomogram based on the characteristics of recurrence, which could be used to accurately stratify patients into distinct prognostic subgroups with significantly different PPS rates.

To date, many studies have consolidated that PDAC is a systemic disease (4, 11). Similar results were also obtained in the present study. In this study, most progressions occurred at the first year following surgery, indicating the systemic nature of this disease. Therefore, exploring the timing and patterns of recurrences is important in survival analyses of PDAC. Additionally, compared with OS, PPS was more influenced by recurrence-related factors as opposed to the characteristics of the primary surgery (13). In this study, most included prognostic factors were related to recurrence. Three additional variables—CA19-9, tumor size, and tumor differentiation—were found to be related to primary tumor status, suggesting that these factors have value for PPS estimation in addition to the effects on tumor recurrence.

Similar to previous studies (4, 7), the present study recorded six different types of recurrence patterns. Liver-only metastasis and local recurrence contributed to the majority of tumor

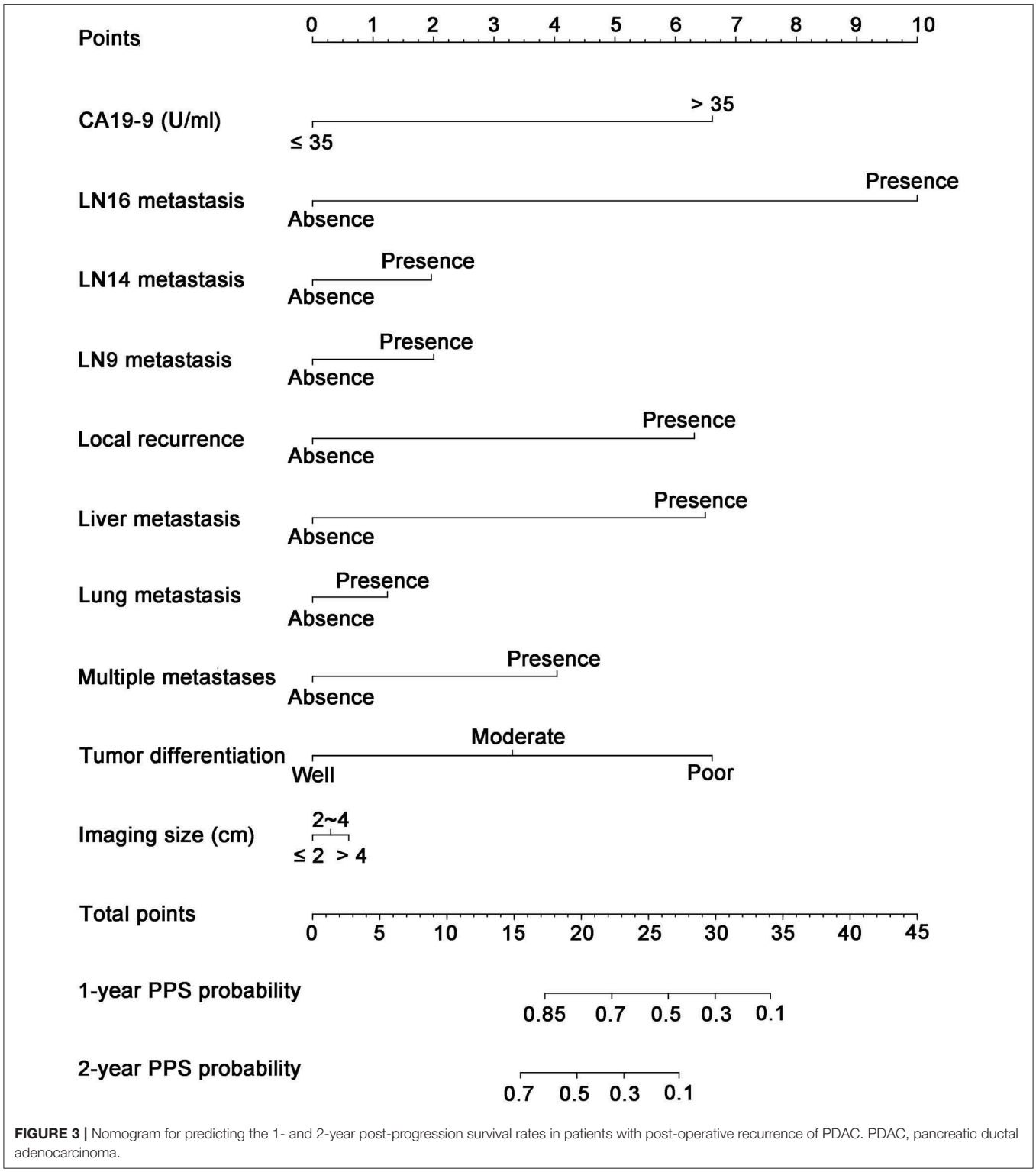

FIGURE 3 | Nomogram for predicting the 1- and 2-year post-progression survival rates in patients with post-operative recurrence of PDAC. PDAC, pancreatic ductal adenocarcinoma.

progressions, with most occurring in the early phase. Multiple metastases and distant metastases at sites apart from liver and lungs contributed to only a small proportion of tumor progressions. However, the presence of multiple metastases indicated the poorest PPS for PDAC patients compared with other types of tumor progressions. Patients with local recurrence had the longest median PPS, followed by patients with lung-only and liver-only metastases. Compared with other types

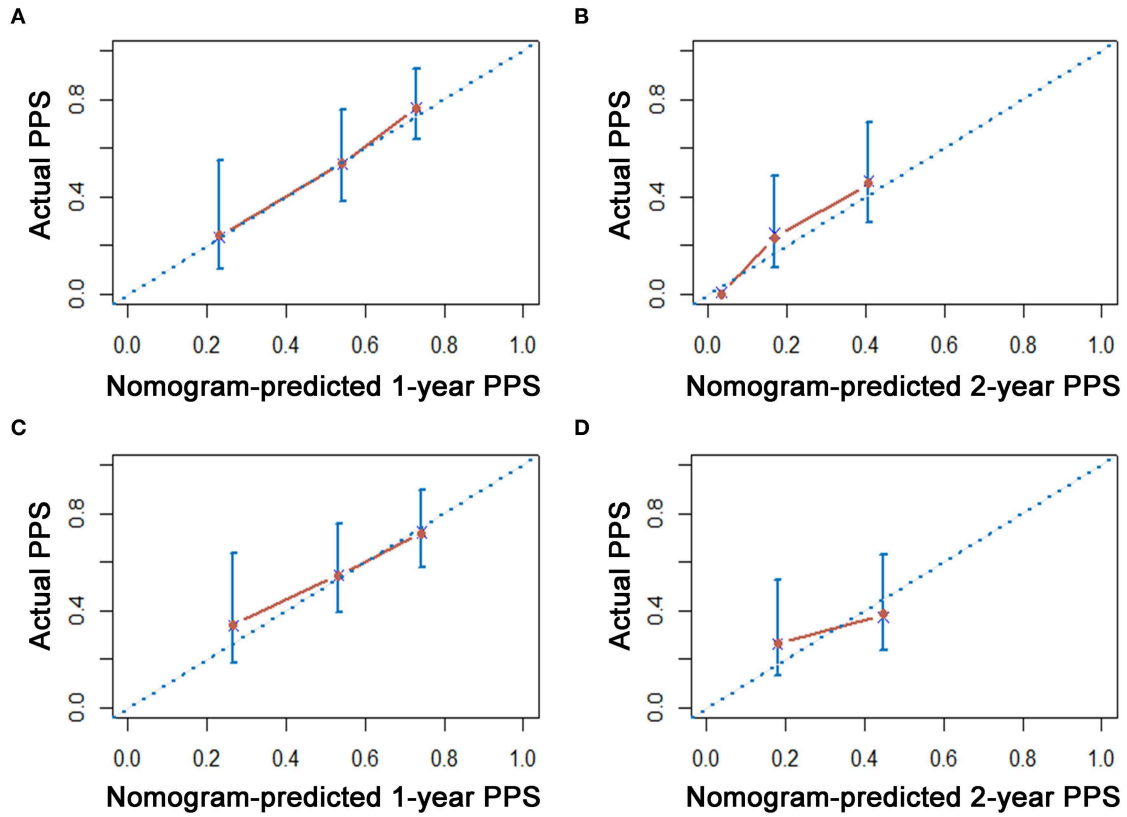

FIGURE 4 | The calibration curve for predicting patient survival at 1 year and 2 years in the training cohort **(A,B)** and validation cohorts **(C,D)**, respectively.

TABLE 3 | Comparison of the C-index and AUC values between nomograms and TNM stage.

System		PPS			
		C-index	AUC		*P*
			1-year	2-year	
Training cohort	Nomogram	0.751 (0.692–0.810)	0.745	0.747	<0.001
	TNM stage	0.602 (0.534–0.680)	0.622	0.618	
Validation cohort	Nomogram	0.710 (0.645–0.775)	0.783	0.748	<0.001
	TNM stage	0.608 (0.536–0.680)	0603	0.619	

PPS, post-progression survival; TNM, tumor–node–metastasis; AUC, area under receiver operating characteristic curve; C-index, concordance index; other abbreviations as in ***Table 1****.*

of tumor progressions, largeness of the tumor bed capacity and the functional preservation of the lungs or liver in lung or liver metastases were helpful for obtaining longer survival times after tumor progressions. Moreover, lung-only and liver-only metastases shared similar survival rates. A 48 high-dimensional radiological and pathological data was incorporated into the LASSO regression, showing that LN9 metastasis, LN14 metastasis, LN16 metastasis, tumor differentiation, imaging-detected tumor size, local progression, liver-only metastasis, lung-only metastasis, and multiple metastases were independent prognostic factors for PPS in PDAC patients following surgery. Moreover, multivariate analysis showed that CA19-9 was also an independent prognostic factor for PPS in these patients. In the Japanese Pancreas Society staging systems for pancreatic cancer, the para-aortic LN16 is categorized as a Group 3 LN station. LN16 metastasis is considered indicative of distant metastasis and poor survival in PDAC (14). LN16 positivity is common in PDAC, and a standard lymphadenectomy of positive LN16 is helpful in elevating survival and has demonstrated the great impact of LN16 metastasis on PPS in PDAC patients (15). Compared with the other variables included in the present study, LN16 metastasis had the greatest impact on PPS, followed by liver-only metastasis, local recurrence, and multiple metastases. The distant genetic signatures of metastatic

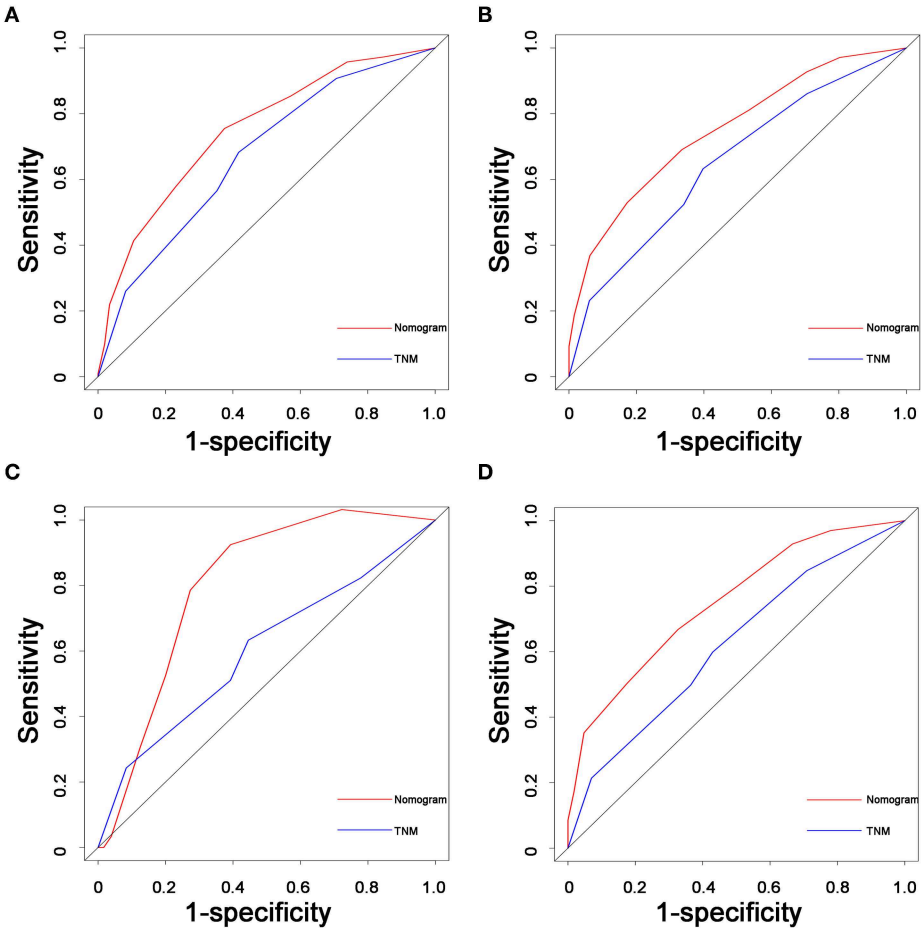

FIGURE 5 | Comparisons of receiver operating characteristic (ROC) curves of both the nomogram and TNM stage system for predicting 1- and 2-year PPS in the training cohort **(A,B)** and validation cohorts **(C,D)**, respectively. TNM, tumor–node–metastasis; PPS, post-progression survival; PDAC, pancreatic ductal adenocarcinoma.

lesions might contribute to organ-specific metastases, and the exploration of their mechanisms could potentially illuminate personal therapeutic approaches.

Apart from the progression patterns, increased CA19-9 levels and tumor largeness were important characteristics of high tumor burden in PDAC, which indicated poor treatment response and early progression (16, 17). Poorly differentiated tumors indicated poor survival as well. A previous study indicated that poorly differentiated tumors release certain molecules, including epidermal growth factor and E-cadherin, which could enhance the development of distant metastases and shorten survival times (18). Compared with pathological tumor size, imaging-detected tumor size was more heavily weighted in the survival analysis and was considered an independent prognostic factor for PPS. The calculation or evaluation of the largest tumor size through image comparisons of different levels of tumors with a 1-mm interval was considered comprehensive and accurate. However, the measurement of the largest pathological tumor size was slightly more subjective, as it was nearly impossible to compare tumor sizes from each level of tumors. This may explain the greater role of imaging-detected tumor size compared with pathological size in predicting survival. In addition, the patients included in this study were from 2008 to 2018 and received no neoadjuvant chemotherapy. Following surgery, 142 patients received adjuvant chemotherapy and 160 patients did not receive adjuvant chemotherapy. Moreover, most of the patients were in the relatively early stages of PDAC (TNM I and II); this may explain the insignificance of chemotherapy in the survival analysis. Further evaluation of the prognostic value of chemotherapy in PDAC is needed.

A nomogram for PPS estimation was established based on these independent prognostic factors, which were selected by evaluating high-dimensional radiological and clinicopathological variables. Compared with traditional nomograms for survival prediction among PDAC patients, our nomogram relied on factors related to recurrence and more precisely indicated survival after tumor progression. Additionally, compared with the 8th TNM stage system, the presently developed predictive nomogram showed higher AUC and C-indexes values and

stronger predictive power for PPS in both training and validation cohorts. The inclusion of specific indicators of progression patterns in addition to primary tumor characteristics ensured that the nomogram would display better discrimination power. Further, the relatively large cohort size of the present study could have made these results more generalizable than those from single-center studies with smaller numbers of patients. Physicians can use this nomogram to assess a variety of parameters with objectivity and precision and to distinguish between different subgroups of PPS among patients with PDAC following radical resection. Therefore, the presently established nomogram can be used as a practical tool to predict survival after tumor progression and has the potential for use in decision-making regarding the subsequent treatment of PDAC patients following surgery. Apart from the precise prediction of survival rates after tumor progression, the established nomogram had indicated several risk factors after surgery, including LN16, LN9, and LN14 metastases, poor tumor differentiation, and higher levels of CA19-9. Patients with these risk factors need to have adjuvant chemotherapy or radiochemotherapy as soon as possible after surgery to prolong survival. Additionally, when recurrence happens, this nomogram indicates that local recurrence and liver metastasis are more likely to lead to poorer survival, compared with lung metastasis. The additional special treatment for recurrence lesions or liver metastasis apart from the conventional chemotherapy, such as tumor ablation, may contribute to better survival for these patients.

The present study had several limitations. First, some variables were unavailable for this study, including specific treatment following surgery as well as the time period and regimen of chemotherapy. The inclusion of these variables could further support the feasibility of the nomogram for use with PDAC patients. Further, it was a limitation for the inclusion of local regression or metastases in that it neglected their time-related nature. Second, it is expected that more tumor progressions would be observed if the follow-up period were extended. Although all the patients were followed for more than 1 year, a longer follow-up period is needed for a more precise overview of tumor progression following surgery. Third, although neoadjuvant chemotherapy is an important factor that may have impacted prognosis, it was not included in the present analysis. Although good fitness was demonstrated for validation in the present study, we should recognize that bootstrapping is only helpful in reducing the overfit bias of the nomogram. More validations using large, independent cohorts are necessary for the validation of the present nomogram.

In conclusion, we compared the PPS of different progression patterns and established a nomogram to predict PPS in patients with postoperative recurrence of PDAC. Validation based on training and validation cohorts showed that this nomogram has great predictive power for survival. The exploration of risk factors and the establishment of this nomogram could illustrate new versions of personalized recurrence management for PDAC patients following surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SL was responsible for the conception, design, and quality control of this study, reviewed and edited the manuscript. CH, SS, and YZ performed the study selection, data extraction, and statistical analyses and were major contributors in writing the manuscript and contributed to the writing of the manuscript. CH and SS participated in study selection and statistical analyses. CH, SS, YZ, and XL contributed in classification criteria discussion. All authors have read and approved the final version of the manuscript.

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Conflict of Interest: 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.

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Association of Mu-Opioid Receptor (MOR) Expression and Opioids Requirement With Survival in Patients With Stage I-III Pancreatic Ductal Adenocarcinoma

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Background: The use of opioids in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) is associated with shorter survival and not dependent on the expression of the mu-opioid receptor (MOR). The role of opioid use and MOR expression in stage I-III PDAC has not been investigated.

Methods: We conducted retrospective study in patients with stage I-III PDAC. MOR expression and *OPRM1* gene expression in tumour tissue and non-tumour tissue was measured. Primary endpoints were overall survival (OS) and disease-free survival (DFS). Secondary endpoints included perineural invasion, intraoperative sufentanil consumption, and length of stay. We performed a subgroup group analysis to evaluate the interaction between levels of MOR expression, amount of opioids use (high *versus* low) and its association with survival.

Results: A total of 236 patients were enrolled in this study.There were no significantly difference in OS rates in patients with high *versus* low levels of MOR (1-year OS: 65.2% *versus* 70.6%, P=0.064; 3-year: 31.4% *versus* 35.8%, P=0.071; 5-year: 19.4% *versus*. 16.2%, P=0.153, respectively) in the tumours. The DFS rates between the groups were no significantly difference. Of note, a high expression of MOR combined with high opioid consumption was associated with poor prognosis in stage I-III PDAC patients. Tumor expressing high levels of MOR show higher rates of perineural invasion.

Conclusion: MOR is not an independent predictor of poor survival in stage I-III PDAC but associated with perineural invasion. Patients requiring high amounts of opioids intraoperatively show worse outcome if they are expressing high levels of MOR.

Keywords: mu-opioid receptor, OPRM1, opioids, pancreatic cancer, overall survival

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers worldwide (1). Owing to the lack of appropriate methods for early detection, the five years survival rate for PDAC is only 8% (2). This worrisome statistic highlights the need of identifying actionable tumour targets to achieve better oncologic control of the disease and thus prolong the survival of patients with PDAC.

In patients with early stage PDAC, surgery is still the treatment of choice (3).

Opioids are still the main analgesics administered to provide adequate pain control during and after PDAC surgery (4). Opioids act on the mu-opioid receptor (MOR) to produce analgesia; however, the receptor is also located in cancer cells such as PDAC cells (5). Over the past few years, there has been increasing interest to elucidate whether MOR or its encoding gene *OPRM1* can be used as predictive biomarkers in different cancers (5). Studies indicate that a high expression of MOR in malignant specimens were associated with worse survival outcome in patients with lung cancer, hepatocellular carcinoma, and laryngeal squamous cell carcinoma (6–8). However, other studies have found that high levels of expression of MOR were not associated with poor prognosis in colorectal and oesophageal squamous cell carcinomas (9, 10). The prognosis significance of MOR expression in PDAC has been recently investigated in patients with advanced disease (11). While a retrospective study demonstrated that the expression of MOR did not impact the prognosis, a high opioid consumption was associated with decreased survival (11).

The association of MOR expression and long-term outcomes in patients with non-metastatic pancreatic cancer is still unclear. We conducted a retrospective study to assess the association between MOR expression levels and long-term outcomes in non-metastatic PDAC patients. We hypothesized that MOR expression is increased in pancreatic cancers in comparison to normal pancreatic tissue and is associated with shorter long-term survival. Furthermore, we investigated the association between MOR expression and perineural invasion, intraoperative opioids consumption and hospital stay.

MATERIALS AND METHODS

Study Population

We conducted retrospective analysis after obtaining approval from Fudan University Shanghai Cancer center (Protocol#2020106-1). We included patients scheduled for pancreatectomy from January 2015 to December 2017. All patients included in the study signed an informed consent after being admitted to the hospital. Inclusion criteria included as follows: (a) surgery for stage I-III PDAC; (b) R0 resection for confirmed PDAC; and (c) no history of another malignant tumour. We excluded patients who died within 30 days of surgery complications and those without complete clinicopathological and follow-up data.

Measurements and Outcomes

The primary outcomes of this research were overall survival (OS) and disease-free survival (DFS). OS was defined as the period from the end of the pancreatic surgery to death or the last follow-up date. DFS was defined as the period from the date of surgery to the date of tumour recurrence or December 2019. Secondary outcomes included perineural invasion, intraoperative sufentanil consumption, and duration of hospital length of stay (LOS).

Anaesthesia Care

In the operating room, patients were routinely monitored according to American Society of Anaesthesiologists (ASA) standards. Induction of general anaesthesia was performed with target-controlled infusion propofol (3.0-4.0μg/ml), sufentanil (0.3-0.5μg/kg), and rocuronium (0.5mg/kg). After induction of general anaesthesia, patients were intubated and anaesthesia was maintained with 2.0-3.0% sevoflurane in mixture oxygen/air. Sufentanil and rocuronium were given intravenously during the surgery according to clinical judgment.

Immunohistochemistry

PDAC tissue fixed on paraffin blocks were obtained for immunohistochemistry (IHC). IHC staining was performed as previously described (8). Briefly, the anti-Mu Opioid Receptor (UMB3)-C-terminal (ab134054) antibody was used in a concentration of 1:200. Secondary antibodies anti-Goat Anti-Rabbit IgG H&L (HRP) (ab205718) were used. Two investigators (physician pathologists) blinded to the data were asked to assessed and scored MOR expression based on previously published criteria (8). The total MOR score was calculated based on staining intensity and proportion of immun0possitive in cancer cells (10).

Impact of OPRM1 on Survival

In addition, we investigated whether mRNA levels of the gene coding for MOR (*OPRM1*) in PDAC were associated with changes in DFS and OS. Briefly, the association of *OPRM1* mRNA expression levels on OS and DFS was assessed *via* Kaplan-Meier Plotter (https://kmplot.com/analysis/). Kaplan-Meier Plotter is a public database containing multiple microarray datasets including GEO, EGA and TCGA (12). The analyses were run on 177 PDAC patients. We included 69 and 146 patients in OS and RFS analyses respectively.

Statistical Analysis

Continuous variables were analysed as mean and standard deviation (SD) or median and interquartile. Frequency counts and percentages were calculated for categorical variables. Univariate associations between MOR expression and clinical variables were tested with Chi-square test. OS and DFS analyses were assessed by Kaplan-Meier methods. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were calculated. Univariate Cox proportional hazards models were fitted to evaluate the effects of continuous variables on the time-to-event outcomes. Multivariable Cox proportional hazard models were used including important and significant covariates. In order to

reduce bias during selection, a propensity score matching analysis was performed to compare OS and DFS between patients who have high *versus* low levels of MOR expression. Patients were matched using a 5-to-1 digit Greedy match algorithm. Eight variables were used in the model including age, ASA physical status, tumour differentiation, Charlson comorbidity index (CCI), Tumor Nodes Metastasis (TNM) stage, surgery type, tumour location and administration of adjuvant chemotherapy. Mean cut-off values for MOR expression and intraoperative opioids consumption were used for subgroup survival analysis using X-tile software (13). For *OPRM1* analysis, the Log-rank test with 95% confidence interval and p values were automatically calculated by the Kaplan-Meier Plotter software. Statistical analyses were performed with SPSS version 17.0. A P value < 0.05 was considered statistically significant.

RESULTS

Four-hundred and twenty-seven patients were screened for this study. After meet exclusion criteria, 146 patients were excluded because of concomitant cancers (n=27); distant metastasis (n=69); chronic inflammatory diseases (n=26) and missing follow-up data (n=24). Two-hundred eighty-one patients were finally included in analysis (**Supplementary Figure 1A**). Baseline demographic and tumour characteristics are shown in **Table 1**. MOR expression levels were not significantly associated with age (P=0.726), gender (P=0.893), CCI (P=0.946), tumour differentiation (P=0.727), tumour size (P=0.757), TNM stage (P=0.766) and tumour location (P=0.446) (**Table 1**).

Immunohistochemistry studies showed no significant differences between MOR expression levels in the tumour and adjacent non-tumour tissues (P=0.378, **Figure 1A**). Similarly, there were no significantly differences between normal and tumour tissue in *OPRM1* expression levels (P=0.429, **Figure 2A**).

Primary Outcomes

The median follow-up time for patients included in the analysis was 15.8 months (95%CI, 13.4, 16.7). After propensity score matching, there were no significantly difference in 1-, 3- and 5-year OS between patients with high *versus* low levels of expression MOR (1-year OS: 65.2% *versus* 70.6%, P=0.064; 3-year: 31.4% *versus* 35.8%, P=0.071; 5-year: 19.4% *versus* 16.2%, P=0.153, respectively, **Figure 3A**). The univariate Cox regression analysis showed that poor tumour differentiation (P<0.001), perineural invasion (P<0.001), and lack of adjuvant chemotherapy (P<0.001) were associated with worse OS (**Table 2**). Also, poor tumour differentiation (HR: 1.85, 95%CI: 1.06, 2.32, P=0.019), nerve invasion positive (HR: 1.58, 95%CI: 1.13, 1.61, P=0.042), and no postoperative chemotherapy (HR: 1.64, 95%CI: 1.02, 1.78, P<0.001) were independent predictors of reduced OS after adjusting for clinical and histopathological factors (**Table 3**). The association between high MOR expression and OS was not statistically significant in the model (HR: 1.08, 95%CI: 0.96, 1.38, P=0.125, **Table 3**). The *OPRM1* gene expression level did not significantly affect OS (P=0.065, **Figure 3C**).

Similarly, there were no significantly difference in DFS when comparing MOR high *versus* MOR low expression levels (1-year DFS: 40.6% *versus* 38.9%, P=0.248; 3-year: 8.6% *versus* 8.1%, P=0.657; 5-year: 2.5% *versus* 2.2%, P=0.843, respectively, **Figure 3B**). The univariate Cox regression analysis showed that patients with poor tumour differentiation (P<0.001), perineural invasion (P<0.001), and those not receiving adjuvant chemotherapy (P<0.001) had a reduced DFS (**Table 2**). In the multivariate analysis, poor tumour differentiation (HR: 2.02, 95%CI: 1.02, 2.42, P=0.027), perineural invasion (HR: 1.75, 95%CI: 1.10, 1.86, P=0.032), and no postoperative chemotherapy (HR: 1.54, 95%CI: 1.32, 1.70, P<0.001) were also significantly associated with poor DFS. The association between high MOR expression and DFS remained no statistically significant (HR: 1.19, 95%CI: 0.94, 1.43, P=0.167, **Table 3**). *OPRM1* analysis showed similar results (P=0.15, **Figure 3D**).

Secondary Outcomes

The mean intraoperative sufentanil consumption was significantly higher in patients with high levels of MOR in their tumours (65.34 ± 4.80μg) than in those with cancers expression low levels of the receptor (45.60 ± 4.60μg) (P<0.001, **Figure 1A**). In terms of hospital LOS, the median duration 16.2 (14.6, 19.2) days in patients with high expression of MOR in their cancers, whereas the median LOS of those in the low MOR expression group was 15.8 (14.8, 18.7) days (P=0.597, **Figure 1B**).

Since PDACs are known to invade nerves and cause significant pain, we investigated the association between MOR expression and perineural invasion (**Figure 2B**). Interestingly, we found that a high expression of MOR was associated with higher rates of perineural invasion (72.9% *versus* 55.1%, P=0.036, **Figure 2B**). We also evaluated the association between survival and MOR expression in relation to opioids consumption (**Figures 1C, D**). Compared to the high MOR expression and high opioids (HMHO) consumption group, the OS of patients with low MOR expression in their tumours and low opioids (LMLO) consumption group was significantly longer (P=0.046, **Figure 1C**). Similarly, compared to the HMHO group, DFS in the LMLO group was significantly better than HMHO group (P=0.039, **Figure 1D**).

DISCUSSION

In this study, we aimed to investigate the impact of MOR and *OPRM1* gene expression on OS and DFS in PDAC patients who were candidate for curative surgery. The multivariate analysis indicated that high levels of MOR or *OPRM1* expression in PDAC tumours were not associated with worse OS and DFS. Our results are in agreement with findings recently reported by Steele at al. in 103 patients with advanced PDAC (11). Also, Oscar Díaz-Cambronero et al. found that there was no association between high expression and lower 5-year OS and DFS in colorectal cancers (10). In a cohort of 239 patients with

TABLE 1 | Baseline characteristics of patients in both groups.

Variable	Original cohort		*P*	Matched cohort		*P*	Standard difference
	MOR high expression group (n=145)	MOR low expression group (n=136)		MOR high expression group (n=118)	MOR low expression group (n=118)		
Age (media-IQR, year)	56 (45-63)	55 (46-67)	0.726	56 (46-62)	56 (46-66)	0.684	3.15
Gender (n, %)							
Female	48 (33.2%)	44 (32.0%)	0.893	42 (35.6%)	43 (36.4%)	0.892	–
Male	97 (66.8%)	92 (68.0%)		76 (64.4%)	75 (63.6%)		–
BMI kg/m2, (median-IQR)	23.5 (21.3-24.3)	22.6 (20.8-24.8)		22.3 (21.3-23.9)	23.0 (20.7-24.3)		–
ASA (n, %)			0.881			0.948	2.58
I	94 (65.2%)	89 (65.4%)		76 (64.4%)	74 (62.7%)		–
II	38 (26.4%)	37 (27.2%)		35 (29.6%)	36 (30.5%)		–
III	13 (8.4%)	10 (7.4%)		7 (6%)	8 (6.8%)		–
Patients enrolled			0.969			0.915	–
2015	50 (34.5%)	46 (33.6%)		39 (33.1%)	41 (34.7%)		
2016	47 (32.4%)	46 (33.8%)		38 (32.2%)	39 (33.1%)		
2017	48 (33.1%)	44 (32.6%)		41 (34.7%)	38 (32.2%)		
CCI (n, %)			0.946			0.861	2.89
0	91 (62.8%)	87 (63.9%)		79 (66.9%)	75 (63.5%)		–
1	43 (29.7%)	38 (27.8%)		30 (25.4%)	33 (27.9%)		
≧2	11 (7.5%)	11 (8.3%)		9 (7.7%)	10 (8.9%)		
Tumor differentiation (n, %)			0.727			0.893	3.26
Well-moderate	53 (36.8%)	47 (34.8%)		43 (36.4%)	44 (37.3%)		–
Poor	92 (63.2%)	89 (65.2%)		75 (63.6%)	74 (62.7%)		–
T stage (n, %)			0.542			0.404	
1	35 (23.9%)	31 (22.8%)		30 (25.4%)	29 (24.6%)		–
2	95 (65.7%)	85 (62.6%)		80 (67.8%)	75 (63.6%)		–
3	15 (10.4%)	20 (14.6%)		8 (6.8%)	14 (11.8%)		–
N stage (n, %)			0.914			0.836	
0	60 (41.2%)	55 (40.5%)		54 (45.7%)	52 (44.1%)		–
1	56 (38.7%)	51 (37.6%)		51 (43.2%)	50 (42.4%)		–
2	29 (20.1%)	30 (21.9%)		13 (11.1%)	16 (13.5%)		–
AJCC 8th edition TNM stage (n, %)			0.766			0.392	4.15
I	70 (48.8%)	63 (46.5%)		54 (45.7%)	52 (44.1%)		–
II	56 (38.7%)	51 (37.9%)		52 (44.1%)	47 (39.8%)		–
III	19 (12.5%)	22 (15.6%)		12 (10.2%)	19 (16.1%)		–
Tumor size (n, %)			0.757			0.613	3.69
≤2 cm	110 (75.8%)	101 (74.2%)		98 (83.1%)	95 (80.5%)		–
>2 cm	35 (24.2%)	35 (25.8%)		20 (16.9%)	23 (19.5%)		–
Surgery type (n, %)			0.660			0.628	3.54
Pancreaticoduodenectomy	82 (56.7%)	74 (54.7%)		71 (60.2%)	68 (57.6%)		–
Distal pancreatectomy	46 (31.4%)	41 (30.0%)		34 (28.8%)	32 (27.1%)		–
Total pancreatectomy	17 (11.9%)	21 (15.3%)		13 (11.0%)	18 (15.3%)		–
Tumor location (n, %)			0.446			0.777	4.56
Head of pancreas	99 (68.5%)	87 (64.2%)		83 (70.3%)	81 (68.6%)		
Tail of pancreas	46 (31.5%)	49 (35.8%)		35 (29.7%)	37 (31.4%)		
Estimated blood loss (n, %)			0.739			0.757	–
≤ 400 ml	106 (73.5%)	97 (71.6%)		92 (77.9%)	90 (76.3%)		–
> 400 ml	39 (26.5%)	39 (28.4%)		26 (22.1%)	28 (23.7%)		–
Blood transfusion			0.858			0.678	–
No	131(90.5%)	122 (89.7%)		104 (88.1%)	106 (89.8%)		
Yes	14 (9.5%)	14 (10.3%)		14 (11.9%)	12 (10.2%)		
Postoperative chemotherapy (n, %)			0.689			0.619	5.21
Yes	122 (84.4%)	112 (82.6%)		97 (82.2%)	94 (79.6%)		–
no	23 (15.6%)	24 (17.4%)		21 (17.8%)	24 (20.4%)		–

BMI, Body Mass Index; IQR, Inter Quartile Range; ASA, American Society of Anesthesiologists score; CCI, Charlson Comorbidity Index; AJCC 8th TNM stage, American Joint Committee on Cancer the 8th edition; MOR, Mu-Opioids Receptor.

esophageal squamous cell carcinoma, the expression of MOR did not affect survival (14). Contrarily, other studies demonstrated that high levels of MOR expression were a marker of worse prognosis in patients with laryngeal and lung cancers (8, 15).

A possible mechanism of opioid-induced cancer progression is via activation MOR and include angiogenesis, tumor-induced inflammation, and facilitation of epithelial-mesenchymal transition (5). Hence, we investigated the association between opioids consumption, MOR expression

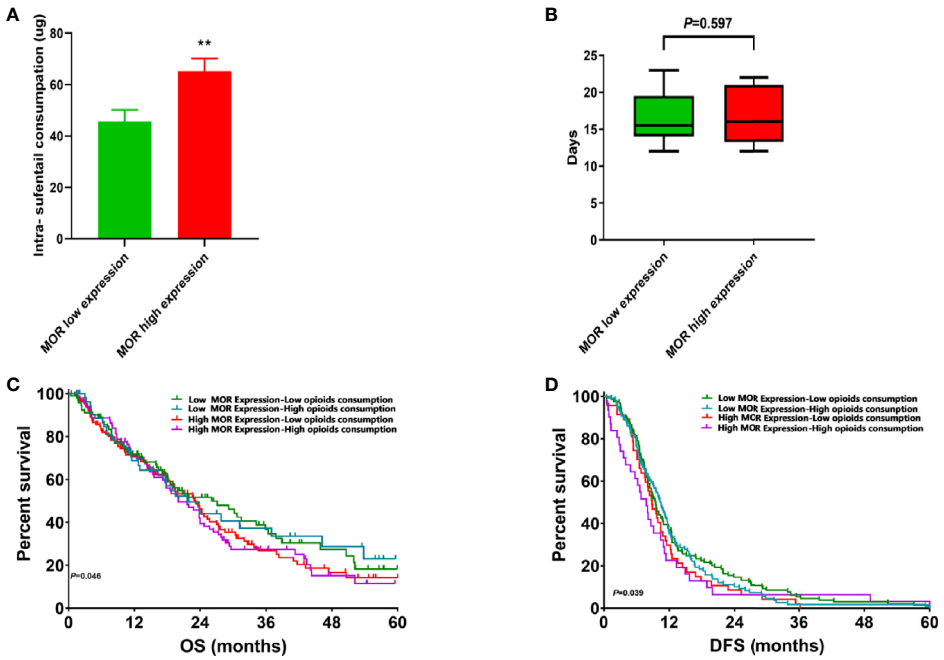

FIGURE 1 | **(A)** Intraoperative sufentanil consumption according to MOR expression; **(B)** Length of stay according to MOR expression; **(C)** Subgroup analysis of OS curves according to MOR expression and opioids consumption. **(D)** Subgroup analysis of DFS curves according to MOR expression and opioids consumption. **P < 0.05

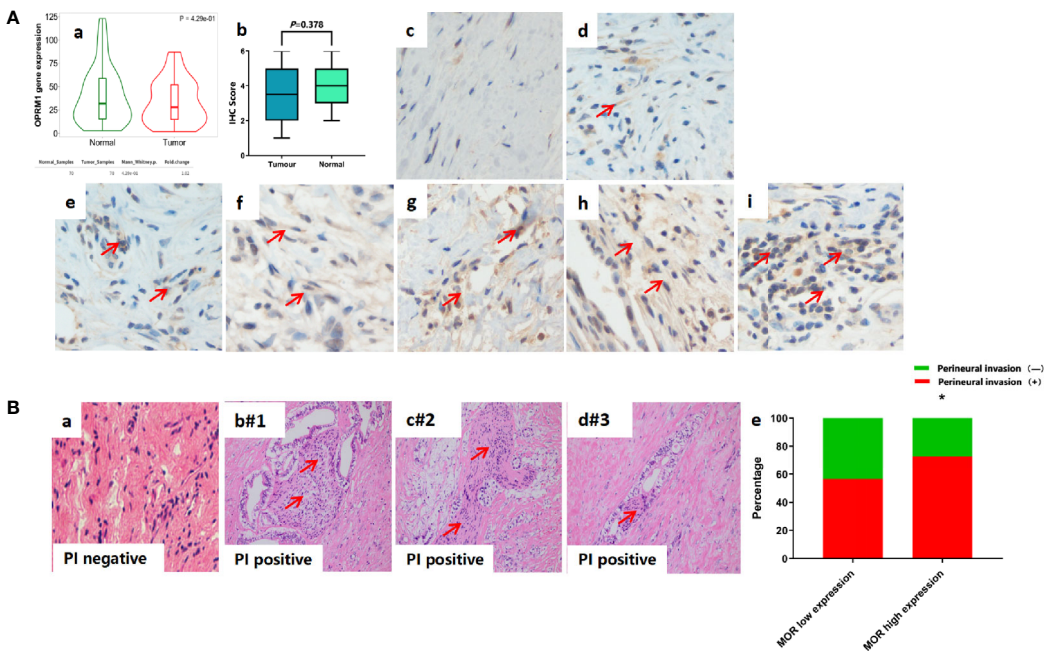

FIGURE 2 | **(A)** Representative image of IHC sample to describe scoring and MOR expression. All images are magnitude 400. (a) OPRM1 gene expression in PDAC tumour tissue and adjacent non-tumour tissue; (b) MOR expression in PDAC tumour tissue and adjacent non-tumour tissue; (c) score 0; (d) score 1; (e) score 2; (f) score 3; (g) score 4; (h) score 5; (i) score 6. **(B)** Representative image of HE staining sample to describe Perineural invasion (PI). (a) PI negative. (b-d) PI positive patients (#1-3). (e) PI positive according to MOR expression. *P < 0.001.

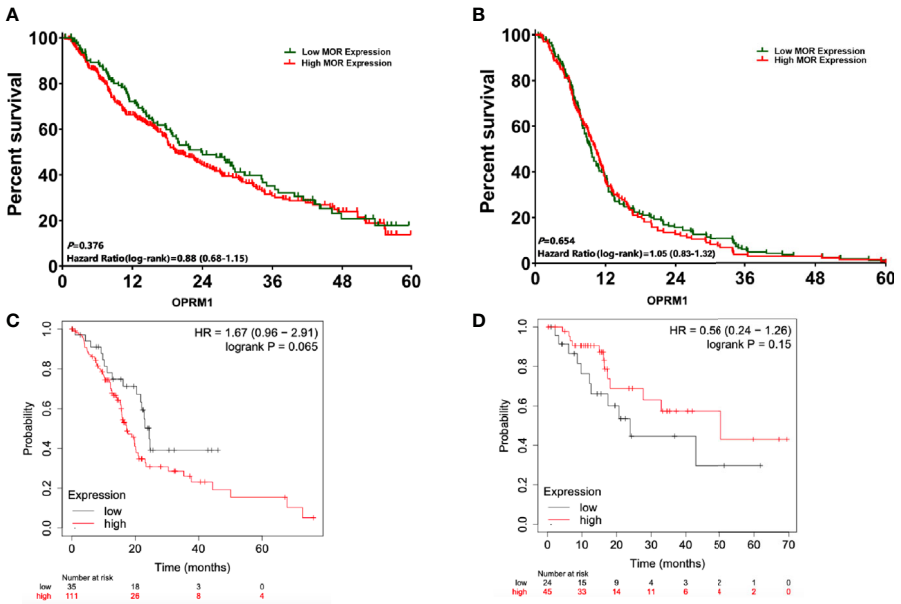

FIGURE 3 | Survival analysis from the date of pancreatic cancer surgery according to expression of MOR and OPRM1. **(A)** OS analysis according to MOR expression; **(B)** DFS analysis according to MOR expression; **(C)** OS curves according to expression of OPRM1 from the cancer database; **(D)** DFS curves according to expression of OPRM1 from the cancer database.

TABLE 2 | Univariate analysis of OS and DFS.

Variables	OS		DFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.02 (0.98,1.21)	0.258	1.08 (0.88,1.32)	0.267
Gender (Male *vs.* Female)	1.11 (0.72,1.52)	0.324	1.05 (0.94,1.11)	0.451
ASA score (1 *vs.* 2. *vs.* 3)	1.05 (0.70,1.46)	0.159	1.11 (0.98,1.16)	0.298
CCI (0 *vs.*1 *vs.* ≧2)	1.15 (0.64,1.20)	0.267	1.26 (1.08,1.61)	0.187
Tumour differentiation (Poor)	2.10 (1.71,2.76)	<0.001	2.34 (1.58,2.65)	<0.001
Nerve invasion (Yes)	1.52 (1.24,1.75)	<0.001	1.63 (1.35,1.81)	<0.001
AJCC TNM stage (I *vs.* II *vs.* III)	1.45 (0.93,1.71)	0.254	1.34 (0.98,1.71)	0.186
Postoperative Chemotherapy (No)	1.42 (1.29,1.58)	<0.001	1.64 (1.38,1.81)	<0.001
MOR expression (high)	1.12 (0.94,1.46)	0.078	1.18 (0.97,1.24)	0.175

BMI, Body Mass Index; IQR, Inter Quartile Range; ASA, American Society of Anaesthesiologists score; CCI, Charlson Comorbidity Index; AJCC 8th TNM stage, American Joint Committee on Cancer the 8th edition; OS, Overall Survival; DFS, Disease free Survival; MOR, Mu-Opioids Receptor.

TABLE 3 | Multivariable Cox proportional of OS and DFS.

Variables	OS (Before matching)		OS (After matching)		DFS (Before matching)		DFS (After matching)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Tumour differentiation (Poor)	1.95 (1.10,2.40)	0.034	1.85 (1.06,2.32)	0.019	2.45 (1.02,2.60)	0.034	2.02 (1.02,2.42)	0.027
Nerve invasion (Yes)	1.64 (1.13,1.76)	0.012	1.58 (1.13,1.61)	0.042	1.89 (1.06,1.96)	0.019	1.75 (1.10,1.86)	0.032
Postoperative Chemotherapy (No)	1.54 (1.01,1.98)	<0.001	1.64 (1.02,1.78)	<0.001	1.63 (1.22,1.79)	<0.001	1.54 (1.32,1.70)	<0.001
MOR expression (high)	1.25 (0.93,1.70)	0.264	1.08 (0.96,1.38)	0.125	1.23 (0.90,1.72)	0.326	1.19 (0.94,1.43)	0.167

OS, Overall Survival; DFS, Disease free Survival; MOR, Mu-Opioids Receptor.

and long-term survival in cancer patients. Interestingly, we observed that patients requiring high intraoperative dosages of sufentanil and who also had PDAC tumours expressing high levels of MOR showed worse survival. This finding suggests an interaction between opioid use and MOR expression. Steele et al. reported that patients with metastatic PDAC requiring low dosages (oral morphine equivalents < 5 mg/day) of opioids had a significant longer survival than those being treated with

high amounts (oral morphine equivalents ≥ 5 mg/day) of opioids (11). Of note, in that study patients in the high opioid group showed slightly higher expression of MOR (11). In a retrospective study, Zylla et al. demonstrated that high levels of MOR were associated with large opioid requirements in patients with advanced prostate cancers (16), also suggesting an interaction between MOR expression and opioid use. The results from Steele et al. and Zylla et al. are similar to our findings indicating an association between sufentanil use and higher MOR expression. It is unclear why patients with higher use of opioids show an exaggerated expression of MOR. Under basal conditions, MOR is down-regulated during agonist stimulation by accelerated degradation as well as the reduced receptor biosynthesis (17). This phenomenon is agonist-concentration and time-dependent. However, we could speculate that a dysregulated MOR turnover in malignant cells as the result of an inflammatory tumor microenvironment could explain our findings in which sustain stimulation with an agonist (opioid) impairs receptor desensitization, internalization, and down-regulation (18). Opioid analgesics have been used to manage moderate to severe acute and chronic pain during and after surgery. They are generally safe; however, in certain patients they produce adverse effects such as respiratory depression and vomiting which should be carefully considered.

Our work also demonstrates that while there was no difference between tumour tissue and adjacent tissue on MOR expression, specimens with higher levels of expression had higher perineural invasion. This finding *per se* is novel. Perineural invasion is associated with pain and is a marker of poor prognosis in patients with PDAC (19, 20). It remains from our study unknown why patients with higher levels of MOR had more features of perineural invasion. But, the presence of MOR in the brain has been linked to opioid modulation of neuritogenesis (21). Thus, we can speculate that MOR activation as the result of endogenous or exogenous opioids can trigger the release of soluble factors (i.e., nerve growth factor) that promote neurogenesis within the pancreatic cancer microenvironment (22). In our study, it is unlikely that a short period of exposure to sufentanil would trigger neurogenesis; therefore, we can speculate that elevated concentrations of locally released endorphins in patients with pain could be responsible of a high rate of neuritogenesis and perineural invasion (23). Alternatively, synthetic opioid such as fentanyl could promote neurotigenesis by regulating BNIP3 *via* miR-145-5 (24). BNIP3 pathway has shown to be upregulated in perineural invasion (25). But, none of our patients were taking opioid preoperatively to support this last theory.

Although our study benefit from large samples of stage I-III PDAC patients, we recognized important limitations as follows. First, the retrospective analysis may be associated with bias that have impact on findings. Second, the low rate of events might have limited the statistical power. Third, the fact that only intraoperative opioid use was recorded limits further conclusions on how postoperative opioids might have affected PDAC progression. And last, we did not perform studies to investigate why MOR expression was higher in patients requiring higher dosages of sufentanil or the relationship between the receptor and perineural invasion.

In conclusion, MOR expression was not associated with OS or DFS in stage I-III pancreatic cancer patients. Our results suggested high MOR expression associated with perineural invasion. Further investigations are needed to evaluate whether blockade of MOR during perioperative period might benefits in pancreatic cancer patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fudan University Shanghai Cancer center (Protocol#2020106-1). The patients/participants provided their written informed consent to participate in this study.

AUTHORS CONTRIBUTIONS

Study design: HZ, JC, WC, and CM. Coordination: MDQ, ZS, and AG. Data acquisition: HZ, WC, and AG. Data interpretation: HZ, ZS, AG, and YY. Drafting: HZ, WC, and JC. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.686877/full#supplementary-material

Supplementary Figure 1 | Flowchart detailing the selection process for patients included in this retrospective analysis. **(A)** Flow chart of stage I-III pancreatic patients enrolled in this study; **(B)** Flow chart of stage I-III pancreatic patients clinical and RNAseq data from cancer database.

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Effects of Total Pancreatectomy on Survival of Patients With Pancreatic Ductal Adenocarcinoma: A Population-Based Study

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Background: Total pancreatectomy (TP) seems to be experiencing a renaissance in recent years. In this study, we aimed to determine the long-term survival of pancreatic ductal adenocarcinoma (PDAC) patients who underwent TP by comparing with pancreaticoduodenectomy (PD), and formulate a nomogram to predict overall survival (OS) for PDAC individuals following TP.

Methods: Patients who were diagnosed with PDAC and received PD ($n = 5,619$) or TP ($n = 1,248$) between 2004 and 2015 were selected from the Surveillance, Epidemiology, and End Results (SEER) database. OS and cancer-specific survival (CSS) of the PD and TP groups were compared using Kaplan-Meier method and log-rank test. Furthermore, Patients receiving TP were randomly divided into the training and validation cohorts. Univariate and multivariate Cox regression were applied to identify the independent factors affecting OS to construct the nomogram. The performance of the nomogram was measured according to concordance index (C-index), calibration plots, and decision curve analysis (DCA).

Results: There were no significant differences in OS and CSS between TP and PD groups. Age, differentiation, AJCC T stage, radiotherapy, chemotherapy, and lymph node ratio (LNR) were identified as independent prognostic indicators to construct the nomogram. The C-indexes were 0.67 and 0.69 in the training and validation cohorts, while 0.59 and 0.60 of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system. The calibration curves showed good uniformity between the nomogram prediction and actual observation. DCA curves indicated the nomogram was preferable to the AJCC staging system in terms of the clinical utility. A new risk stratification system was constructed which could distinguish patients with different survival risks.

Conclusions: For PDAC patients following TP, the OS and CSS are similar to those who following PD. We developed a practical nomogram to predict the prognosis of PDAC patients treated with TP, which showed superiority over the conventional AJCC staging system.

Keywords: pancreatic ductal adenocarcinoma, total pancreatectomy, propensity score matching, prognosis, nomogram, SEER

INTRODUCTION

Pancreatic cancer remains a devastating disease. According to the latest reports, pancreatic cancer ranks the fourth in the tumor-related death in the United States in 2020, with the 5-year survival rate of only 9% (1). Pancreatic ductal adenocarcinoma (PDAC) is the most common histopathological type and has almost been synonymous with pancreatic cancer (2). Surgical resection is the only known curative method. As we all know, there are three main surgical approaches for PDAC generally based on the location of the lesion, pancreaticoduodenectomy (PD), distal pancreatectomy (DP) and total pancreatectomy (TP). While PD and DP have been common surgical approaches with confirmed short- and long-term outcomes (3, 4), the role of TP in the treatment of PDAC remains controversial.

TP was first performed by Rockey in 1943 for PDAC, but the patient died of severe bile duct leakage 15 days later (5). TP, a resection of the entire gland, was considered as a more radical surgical method which can effectively avoid potential postoperative pancreatic fistula (POPF) and minimize the risk of tumor recurrence in early period (6). However, TP was then shown to lead to higher perioperative morbidity and mortality than PD (7). Additionally, TP strongly influences patients' metabolic function and postoperative quality of life (QoL) due to permanent pancreatic endo-exocrine insufficiency (8). Despite these adverse effects, TP is still required in some cases to achieve a negative resection margin and complete clearance (9). Several studies have compared perioperative morbidity and mortality between TP and PD, but data on long-term survival benefit between the two surgical methods are still minimal and even controversial (7, 10–14). Since most previous reports were single-center and small sample size investigations, further exploration concerning the long-term survival benefit of TP is needed.

PDAC is heterogeneous among individuals regarding survival, so a practical and personalized prognostic tool that can predict the survival probability is necessary and helpful. The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system has been commonly used for prognostic prediction after surgery (15). However, the TNM staging system includes only lesion size, positive lymph nodes on pathological examination, and presence of distant metastasis. Other factors such as age, sex, serum carbohydrate antigen 19-9 (CA 19-9), tumor differentiation, lymph node ratio (LNR), and even marital status are also considered to be related to the prognosis of PDAC (16–19).

Nomogram models are novel, simple and convenient mathematical tools for prognostic prediction in clinical practice; it incorporates important demographic and clinicopathological characteristics to forecast individual prognosis more precisely (20). The Surveillance, Epidemiology, and End Results (SEER) in the United States is a long-established and open access database providing population-based statistics and information on various cancers. In this study, by using data of SEER, we were aiming to probe the long-term survival of PDAC patients who underwent TP by comparing them with those who underwent PD, and also to formulate a prognostic nomogram to better predict overall survival (OS) for PDAC individuals following TP.

MATERIALS AND METHODS

Patients Selection and Data Extraction

This retrospective study focused on patients who were diagnosed with PDAC and treated with PD and TP from 2004 to 2015, with the last follow-up in November 2018. All the subjects were extracted from the SEER database (SEER*Stat 8.3.9). Patients diagnosed with PDAC were selected using the site codes (C25.0-25.9) and histology codes (8140 and 8500) of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3). Surgery codes of PD and TP were 37 and (40, 60), respectively. The exclusion criteria were as follows: (1) The carcinoma had metastasized; (2) incomplete or absence information about survival time, overall life status, cause of death, or other characteristics; (3) non-primary tumor; (4) age at diagnosed < 18 years old. Demographic and clinicopathological data, including age, sex, race, marital status, surgical methods, tumor location, size, differentiation, T and N stage of AJCC system, LNR, radiotherapy, chemotherapy, survival time, death reasons, and living status were extracted from the dataset.

The value of LNR was defined as the ratio of the number of positive lymph nodes to the total number of examined nodes. Overall survival (OS) was defined as the time from diagnosis to death due to any cause. Cancer-specific survival (CSS) was defined as the duration from diagnosis to death related to PDAC. The 6th or 7th AJCC TNM stage was transformed into the 8th AJCC TNM stage.

Survival Analysis of TP and PD

We divided the patients according to their surgical treatment. Propensity score matching (PSM) analysis was applied to adjust for confounders and reduce the effect of selection bias (21). The X-tile program (Yale University, New Haven, CT, USA) was used to acquire the best cutoff values of age, tumor size, year and LNR (22). The two groups were matched in a 1:1 ratio using the nearest-neighbor method with a caliper of 0.01.

TABLE 1 | Demographic and clinicopathological characteristics of the patients before and after PSM.

Characteristics	Original cohort (n = 6,867)			Matched cohort (n = 2,496)		
	PD (n = 5,619) n (%)	TP (n = 1,248) n (%)	P-value	PD (n = 1,248) n (%)	TP (n = 1,248) n (%)	P-value
Age (year)			0.81			0.34
≤56	1,137 (20.2)	255 (20.4)		237 (19.0)	255 (20.4)	
57–76	3,636 (64.7)	797 (63.9)		832 (66.7)	797 (63.9)	
≥77	846 (15.1)	196 (15.7)		179 (14.3)	196 (15.7)	
Gender			0.71			0.90
Female	2,877 (51.2)	631 (50.6)		635 (50.9)	631 (50.6)	
Male	2,742 (48.8)	617 (49.4)		613 (49.1)	617 (49.4)	
Marital status			0.82			1.00
Married	3,534 (62.9)	780 (62.5)		779 (62.4)	780 (62.5)	
Other status	2,085 (37.1)	468 (37.5)		469 (37.6)	468 (37.5)	
Race			0.20			0.74
White	4,601 (81.9)	999 (80.0)		1,006 (80.6)	999 (80.0)	
Black	559 (9.9)	129 (10.3)		114 (9.1)	129 (10.3)	
Asian	426 (7.6)	115 (9.2)		122 (9.8)	115 (9.2)	
Other	33 (0.6)	5 (0.4)		6 (0.5)	5 (0.4)	
Tumor location			**<0.001**			1.00
Head	5,086 (90.5)	970 (77.7)		970 (77.7)	970 (77.7)	
Other	533 (9.5)	278 (22.3)		278 (22.3)	278 (22.3)	
Differentiation			0.55			0.27
Well	560 (10.0)	113 (9.1)		115 (9.2)	113 (9.1)	
Moderate	2,953 (52.6)	659 (52.8)		662 (53.0)	659 (52.8)	
Poor	2,057 (36.6)	461 (36.9)		465 (37.3)	461 (36.9)	
Undifferentiated	49 (0.9)	15 (1.2)		6 (0.5)	15 (1.2)	
Tumor size (mm)			0.36			0.78
≤24	1,426 (25.4)	297 (23.8)		283 (22.7)	297 (23.8)	
25–33	1,763 (31.4)	386 (30.9)		386 (30.9)	386 (30.9)	
≥34	2,430 (43.2)	565 (45.3)		579 (46.4)	565 (45.3)	
8th AJCC T stage			0.20			0.62
T1	598 (10.6)	129 (10.3)		133 (10.7)	129 (10.3)	
T2	3,296 (58.7)	697 (55.8)		679 (54.4)	697 (55.8)	
T3	1,502 (26.7)	367 (29.4)		390 (31.2)	367 (29.4)	
T4	223 (4.0)	55 (4.4)		46 (3.7)	55 (4.4)	
8th AJCC *N* stage			0.72			0.54
*N*0	1,698 (30.2)	391 (31.3)		399 (32.0)	391 (31.3)	
*N*1	2,372 (42.2)	522 (41.8)		496 (39.7)	522 (41.8)	
*N*2	1,549 (27.6)	335 (26.8)		353 (28.3)	335 (26.8)	
Chemotherapy			**<0.001**			0.87
No	1,574 (28.0)	413 (33.1)		418 (33.5)	413 (33.1)	
Yes	4,045 (72.0)	835 (66.9)		830 (66.5)	835 (66.9)	
Radiotherapy			**0.04**			0.41
No	3,316 (59.0)	777 (62.3)		798 (63.9)	777 (62.3)	
Yes	2,303 (41.0)	471 (37.7)		450 (36.1)	471 (37.7)	
LNR			0.23			0.65
≤0.06	2,218 (39.5)	525 (42.1)		511 (40.9)	525 (42.1)	
0.07–0.23	1,807 (32.2)	379 (30.4)		372 (29.8)	379 (30.4)	
≥0.24	1,594 (28.4)	344 (27.6)		365 (29.2)	344 (27.6)	

AJCC, American Joint Committee on Cancer; LNR, lymph node ratio; PD, pancreaticoduodenectomy; PSM, propensity score matching; TP, total pancreatectomy. Bold values meant statistically significant.

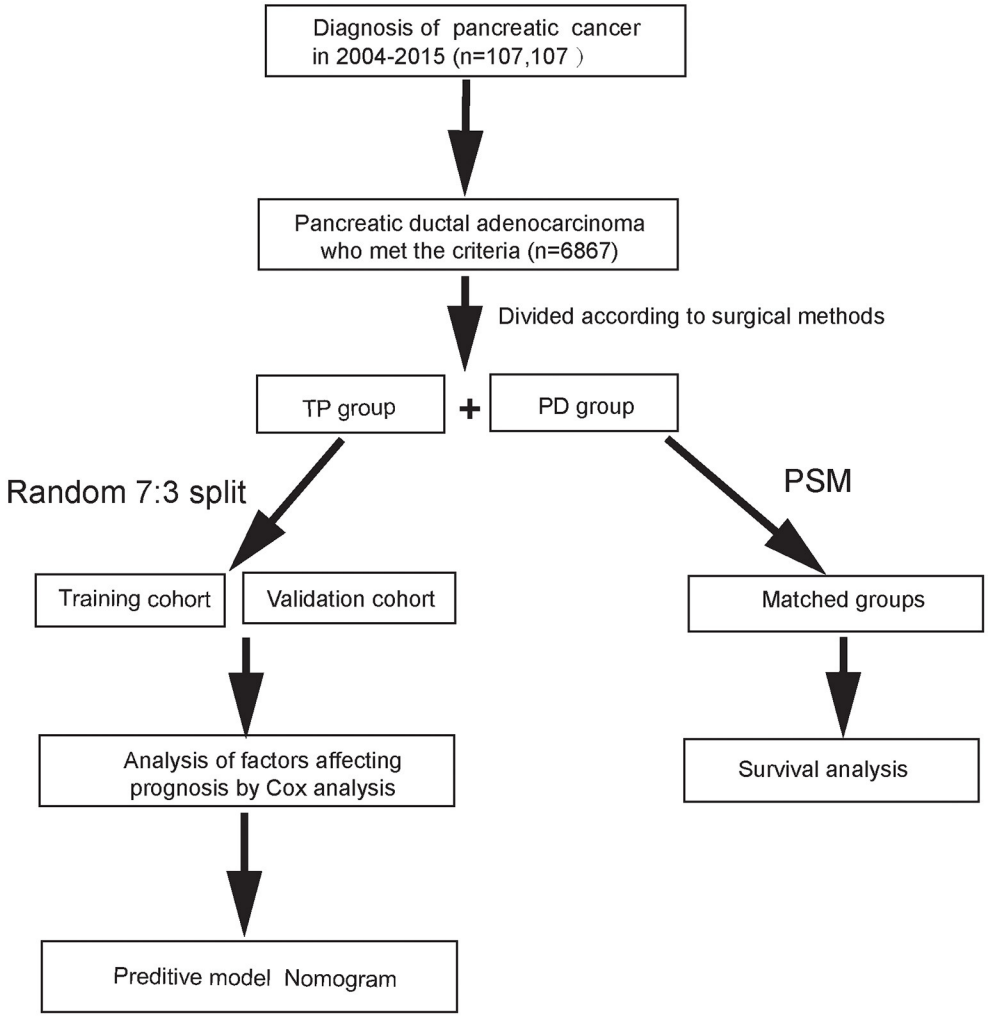

FIGURE 1 | Simple flow diagram of the study.

The Kaplan-Meier method and log-rank test were used for the survival analysis.

Prognostic Nomogram for TP

We randomly divided the patients who underwent TP into the training and validation cohorts at a ratio of 7:3. The nomogram for TP survival prediction was constructed based on the training cohort. Univariate and multivariate Cox proportional-hazards models were used to determine the prognostic factors. Factors in the nomogram for 1-, 3-, and 5-year OS prediction were based on the results of the multivariate Cox regression analysis. The nomogram model was validated by the two cohorts. The discriminative capacity was evaluated by the concordance index (C-index) (23). The C-index ranged from 0.5 to 1, with larger values indicating better prediction accuracy. Calibration was evaluated by drawing calibration curves to investigate the consistency between the predicted probabilities and actual survival outcomes (24). The predictive ability of the nomogram was evaluated using 1,000 bootstrap resamples. Decision curve analysis (DCA), a novel algorithm, was performed to assess the clinical value of the nomogram by quantifying net benefit at different threshold probabilities (25). Moreover, according to the cutoff values calculated by X-tile, the overall scores calculated from the nomogram were classified into three groups, low-risk, intermediate-risk, and high-risk groups. Kaplan-Meier analysis and log-rank test were applied to compare the OS of different groups, testing whether the nomogram model could distinguish patients with different survival risks.

Statistical Analysis

Continuous variables were shown as medians and interquartile range (IQR), while categorical variables were displayed as numbers and percentages. Features of Cox regression were presented as hazard ratio (HR) and corresponding 95% confidence intervals (CI). A student's *t*-test or Mann-Whitney *U*-test was used for continuous variables and chi-square test for categorical variables. Two-tailed P-values < 0.05 were considered

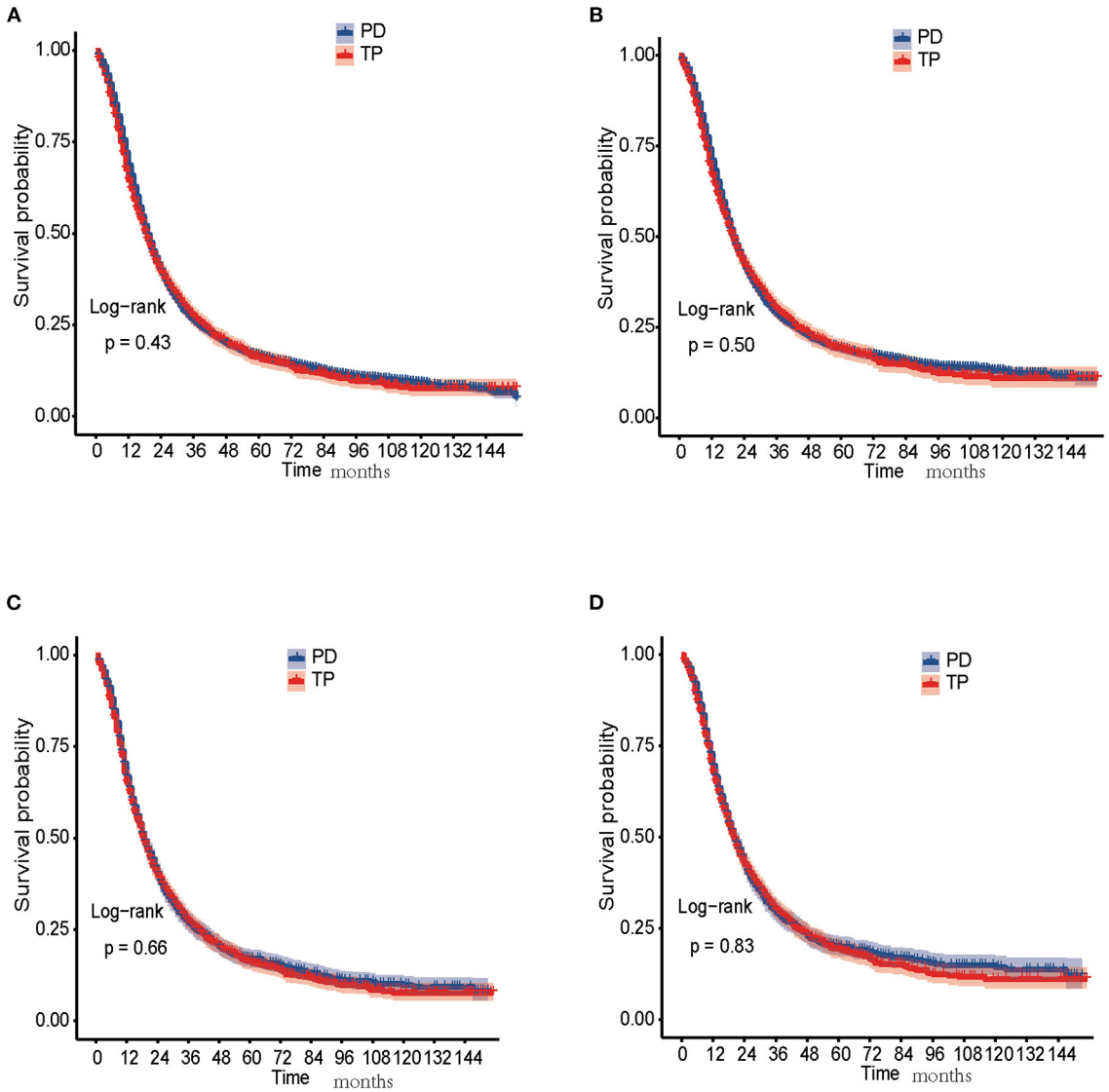

FIGURE 2 | Survival analysis of PDAC patients treated with PD and TP. **(A)** OS curves of PD and TP groups before PSM; **(B)** CSS curves of PD and TP groups before PSM; **(C)** OS curves of PD and TP groups after PSM; **(D)** CSS curves of PD and TP groups after PSM. CSS, cancer-specific survival ; OS, overall survival; PD, pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; PSM, propensity score matching; TP, total pancreatectomy.

statistically significant. Statistical analyses were conducted using R software (version 4.0.1 http://www.r-project.org).

RESULTS

Characteristics of the Included Patients

A total of 6,867 patients with PDAC were screened from the SEER database from 2004 to 2015. Among these patients, 5,619 underwent PD and 1,248 received TP. According to the X-tile program, age was divided into <57 years old, 57–76 years old, and 77 years old or more; tumor size into <25, 25–33, and 34 mm or more; LNR into <0.07, 0.07–0.23, and 0.24 or more (**Supplementary Figures S1A–C**). Features of the patients were displayed in **Table 1**. After a 1:1 PSM, all baseline data were comparable between the two matched cohorts containing 1,248 pairs. **Figure 1** showed the research process of this study.

Treatment Effects of TP vs. PD on Survival

In the unmatched cohort, the 1-, 3-, and 5-year OS rates in the PD group were 68.5, 26.1, and 16.4%, while 64.5, 27.0, and 16.1% in the TP group, respectively. The 1-, 3-, and 5-year CSS rates in the PD group were 70.8, 28.6, and 19.1%, while 67.1, 29.8, and 19.1% in the TP group, respectively. The Kaplan-Meier analysis and log-rank test showed that both OS ($P = 0.43$) and CSS ($P = 0.50$) in the TP and PD groups were similar and no significant differences were found (**Figures 2A,B**).

TABLE 2 | Univariate and multivariate Cox analysis of variables affecting OS for PDAC patients following TP.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (year)						
≤56	Reference			Reference		
57–76	1.15	0.95–1.39	0.15	0.96	0.96–1.42	0.12
≥77	1.56	1.22–1.99	**<0.001**	1.44	1.12–1.86	**0.005**
Gender						
Female	Reference					
Male	1.08	0.93–1.25	0.34			
Marital status						
Married	Reference					
Other status	1.14	0.98–1.32	0.10			
Race						
White	Reference					
Black	0.89	0.69–1.13	0.34			
Asian	0.93	0.71–1.22	0.59			
Other	4.43	0.62–31.62	0.14			
Tumor location						
Head	Reference					
Other	0.93	0.77–1.12	0.45			
Tumor differentiation						
Well	Reference			Reference		
Moderate	1.70	1.25–2.31	**0.001**	1.50	1.10–2.05	**0.01**
Poor	2.65	1.94–3.63	**<0.001**	2.24	1.63–3.09	**<0.001**
Undifferentiated	2.27	1.17–4.38	**0.02**	1.69	0.86–3.33	0.13
Tumor size (mm)						
≤24	Reference			Reference		
25–33	1.87	1.51–2.30	**<0.001**	1.27	0.99–1.63	0.06
≥34	1.78	1.47–2.17	**<0.001**	1.19	0.89–1.58	0.24
8th AJCC T stage						
T1	Reference			Reference		
T2	2.31	1.74–3.07	**<0.001**	1.70	1.21–2.38	**0.002**
T3	2.51	1.87–3.37	**<0.001**	1.93	1.28–2.91	**0.002**
T4	2.93	1.91–4.49	**<0.001**	2.73	1.67–4.46	**<0.001**
8th AJCC *N* stage						
*N*0	Reference			Reference		
*N*1	1.61	1.34–1.93	**<0.001**	1.20	0.90–1.60	0.22
*N*2	2.12	1.73–2.58	**<0.001**	1.19	0.83–1.70	0.35
Chemotherapy						
No	Reference			Reference		
Yes	0.66	0.56–0.77	**<0.001**	0.57	0.47–0.69	**<0.001**
Radiotherapy						
No	Reference			Reference		
Yes	0.79	0.67–0.92	**0.002**	0.83	0.70–0.99	**0.04**
LNR						
≤0.06	Reference			Reference		
0.07–0.23	1.81	1.51–2.17	**<0.001**	1.65	1.24–2.20	**0.001**
≥0.24	2.01	1.68–2.41	**<0.001**	1.86	1.35–2.54	**<0.001**

AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; LNR, lymph node ratio; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; TP, total pancreatectomy. Bold values meant statistically significant.

TABLE 3 | Comparison of characteristics of TP patients in the training cohort and validation cohort.

Characteristics	All TP patients (n = 1,248) n (%)	Training cohort (n = 873) n (%)	Validation cohort (n = 375) n (%)	P-value
Age (year)				0.98
≤56	255 (20.4)	179 (20.5)	76 (20.3)	
57–76	797 (63.9)	556 (63.7)	241 (64.3)	
≥77	196 (15.7)	138 (15.8)	58 (15.5)	
Gender				0.82
Female	631 (50.6)	439 (50.3)	192 (51.2)	
Male	617 (49.4)	434 (49.7)	183 (48.8)	
Marital status				0.71
Married	780 (62.5)	549 (62.9)	231 (61.6)	
Other status	468 (37.5)	324 (37.1)	144 (38.4)	
Race				0.11
White	999 (80.0)	702 (80.4)	297 (79.2)	
Black	129 (10.3)	90 (10.3)	39 (10.4)	
Asian	115 (9.2)	80 (9.2)	35 (9.3)	
Other	5 (0.4)	1 (0.1)	4 (1.1)	
Tumor location				0.46
Head	970 (77.7)	684 (78.4)	286 (76.3)	
Other	278 (22.3)	189 (21.6)	89 (23.7)	
Differentiation				0.47
Well	113 (9.1)	77 (8.8)	36 (9.6)	
Moderate	659 (52.8)	456 (52.2)	203 (54.1)	
Poor	461 (36.9)	327 (37.5)	134 (35.7)	
Undifferentiated	15 (1.2)	13 (1.5)	2 (0.5)	
Tumor size (mm)				0.75
≤24	297 (23.8)	213 (24.4)	84 (22.4)	
25–33	386 (30.9)	268 (30.7)	118 (31.5)	
≥34	565 (45.3)	392 (44.9)	173 (46.1)	
8th AJCC T stage				0.69
T1	129 (10.3)	96 (11.0)	33 (8.8)	
T2	697 (55.8)	482 (55.2)	215 (57.3)	
T3	367 (29.4)	256 (29.3)	111 (29.6)	
T4	55 (4.4)	39 (4.5)	16 (4.3)	
8th AJCC *N* stage				0.81
*N*0	391 (31.3)	272 (31.2)	119 (31.7)	
*N*1	522 (41.8)	362 (41.5)	160 (42.7)	
*N*2	335 (26.8)	239 (27.4)	96 (25.6)	
Chemotherapy				0.96
No	413 (33.1)	288 (33.0)	125 (33.3)	
Yes	835 (66.9)	585 (67.0)	250 (66.7)	
Radiotherapy				0.53
No	777 (62.3)	549 (62.9)	228 (60.8)	
Yes	471 (37.7)	324 (37.1)	147 (39.2)	
LNR				0.14
≤0.06	525 (42.1)	369 (42.3)	156 (41.6)	
0.07–0.23	379 (30.4)	252 (28.9)	127 (33.9)	
≥0.24	344 (27.6)	252 (28.9)	92 (24.5)	

AJCC, American Joint Committee on Cancer; LNR, lymph node ratio; TP, total pancreatectomy.

In the matched cohort, the 1-, 3-, and 5-year OS rates in the PD group were 66.1, 26.2, and 17.0%, while 64.5, 27.0, and 16.1% in the TP group, respectively. The 1-, 3-, and 5-year CSS rates in the PD group were 68.7, 28.8, and 19.6%, while 67.1, 29.8, and 19.1% in the TP group, respectively. No significant differences were detected in both

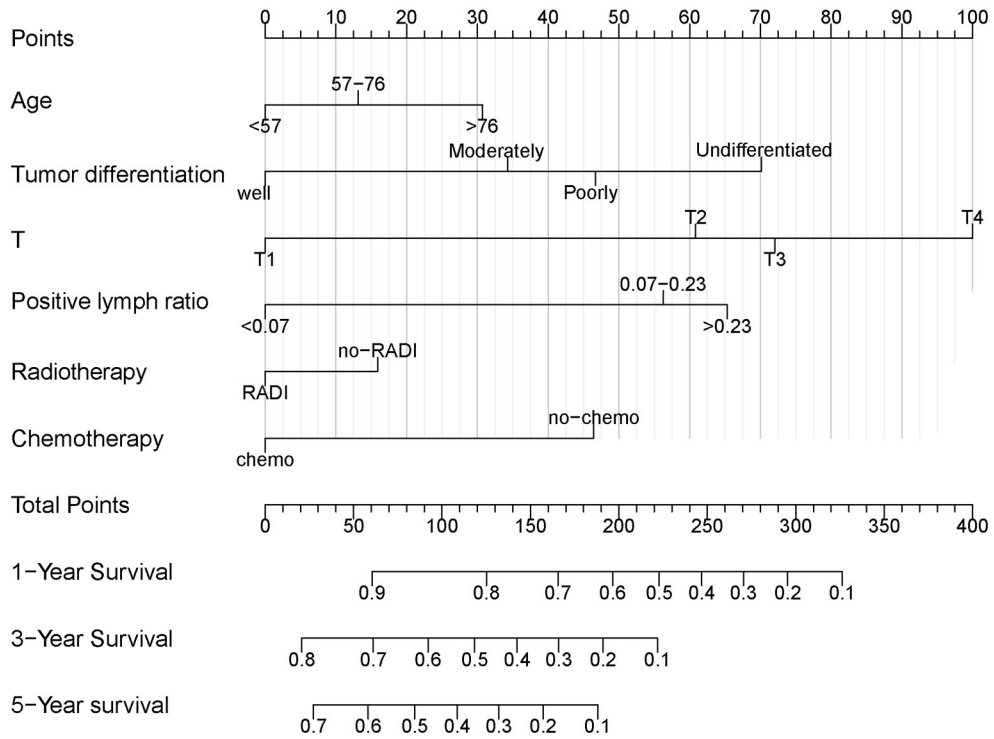

FIGURE 3 | Nomogram for predicting OS of PDAC patients treated with TP. OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; TP, total pancreatectomy.

OS ($P = 0.66$) and CSS ($P = 0.83$) between the two groups (**Figures 2C,D**).

Analysis of Variables and Affecting OS Among TP Patients

Cox regression analysis were operated in the training cohort to determine the prognostic factors for PDAC patients after TP. Univariate analysis identified that age, tumor size, differentiation, 8th AJCC T and N stage, radiotherapy, chemotherapy, and LNR were significantly associated with OS. Additionally, multivariate analysis revealed age, differentiation, 8th AJCC T stage, radiotherapy, chemotherapy, and LNR were independent prognostic indicators (**Table 2**).

Construction and Validation of Nomogram

Independent prognostic variables were selected for developing the nomogram for prognostic prediction of PDAC patients treated with TP. As shown in **Table 3**, the entire TP group was randomly divided into the training and validation cohorts. **Figure 3** demonstrated the nomogram that was used for the 1-, 3-, and 5-year OS probabilities. It could be seen from the nomogram that the AJCC T stage had the greatest impact on OS. The survival probability of an individual was simply acquired by summing all scores for each factor and corresponding to the scores on the total score scale in the nomogram. Higher total scores indicated worse survival probability.

The C-indexes were 0.67 (95% CI: 0.66–0.68) and 0.69 (95% CI: 0.68–0.71) in the training and validation cohorts, respectively. While in the AJCC staging system, the C-indexes were 0.59 (95% CI: 0.58–0.61) and 0.60 (95% CI: 0.58–0.61) in the two cohorts, respectively. As a result, the nomogram had a more favorable discriminatory ability than the AJCC system. The predicted 1- and 3-year OS showed good unanimity with the observed situations both in the two cohorts, according to the calibration plots (**Figures 4A–D**). Furthermore, in both cohorts, the DCA demonstrated that the nomogram could provide satisfactory 1- and 3-year OS predictions with a preferable positive net benefit. Compared with the TNM staging system, the nomogram had better clinical practicality (**Figures 5A–D**).

Risk Stratification Based on the Nomogram

Finally, we performed a survival risk stratification analysis according to the cutoff values of the nomogram scores by using X-tile in the training cohort (**Supplementary Figure S1D**). Patients were divided into three risk groups: low-risk (total score < 123), intermediate-risk (total score: 123–217), and high-risk (total score > 217). The Kaplan-Meier curves showed significant discrimination in OS among the three groups in both cohorts and the whole cohort (**Figures 6A–C**).

DISCUSSION

In this retrospective study, based on the seer database, we conducted a PSM analysis to compare the survival of PDAC patients who were treated with TP and PD. Before and after PSM,

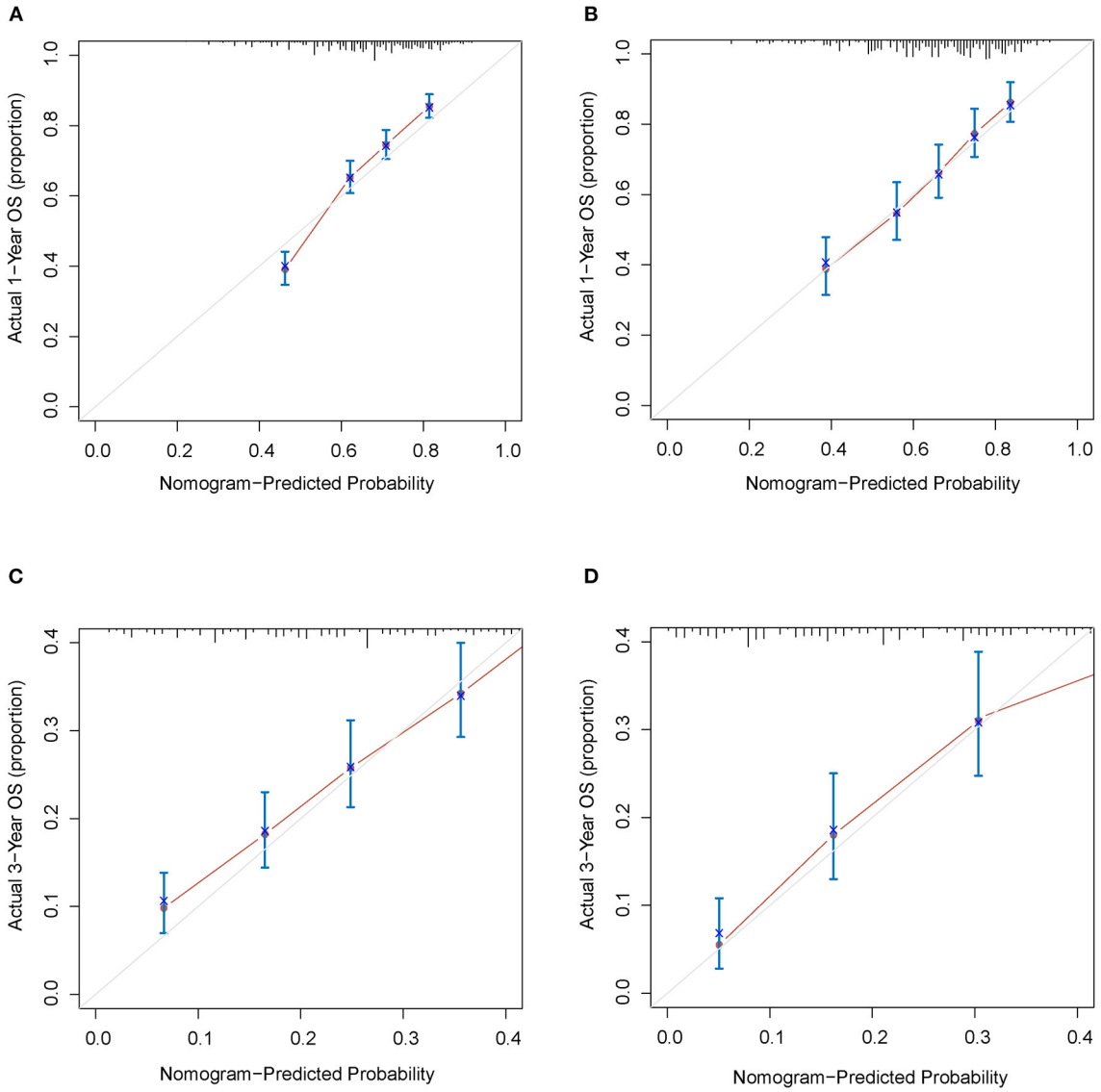

FIGURE 4 | Calibration plots for 1- and 3-years OS of the nomogram. **(A)** Calibration plot of 1-year OS in the training cohort; **(B)** Calibration plot of 1-year OS in the validation cohort; **(C)** Calibration plot of 3-year OS in the training cohort; **(D)** Calibration plot of 3-year OS in the validation cohort. OS, overall survival.

the results consistently showed that PDAC patients following TP had similar OS and CSS compared with those following PD. Additionally, we formulated a nomogram which could effectively forecast the 1-, 3-, and 5-year OS of PDAC patients treated with TP, which might be helpful for clinicians to better grasp their patients' prognostic results. To the best of our knowledge, this is the first time that a nomogram was constructed specifically for PDAC patients treated with TP.

PDAC accounts for an overwhelming majority of pancreatic cancer, which is widely known as "the king of cancers." Surgery plays an essential role and is considered the dominant modality in PDAC treatment. PD remains the most common surgical method for PDAC. Occasionally, PD may be inadequate to achieve complete clearance of the tumor; hence, TP may be required under this circumstance. In the 1960s and 1970s, TP reached its peak and was even regarded as a routine surgical approach for PDAC in many clinical centers (6). However, after the enthusiasm for TP, its disadvantages became obvious. Many surgeons were reluctant to choose TP in the treatment of PDAC due to increased perioperative risks and permanent pancreatic dysfunction. With the development and advances in surgical techniques, progress in researching synthetic insulin and pancreatic enzymes, TP now can be operated safely with acceptable morbidity and mortality compared with PD (26–28), and postoperative QoL has also improved (29). It was previously thought that TP was associated poorer long-term survival compared with PD (7, 14), but several studies have argued that the long-term survival of PDAC patients following TP vs. PD was equivalent (11, 12, 30). These series were

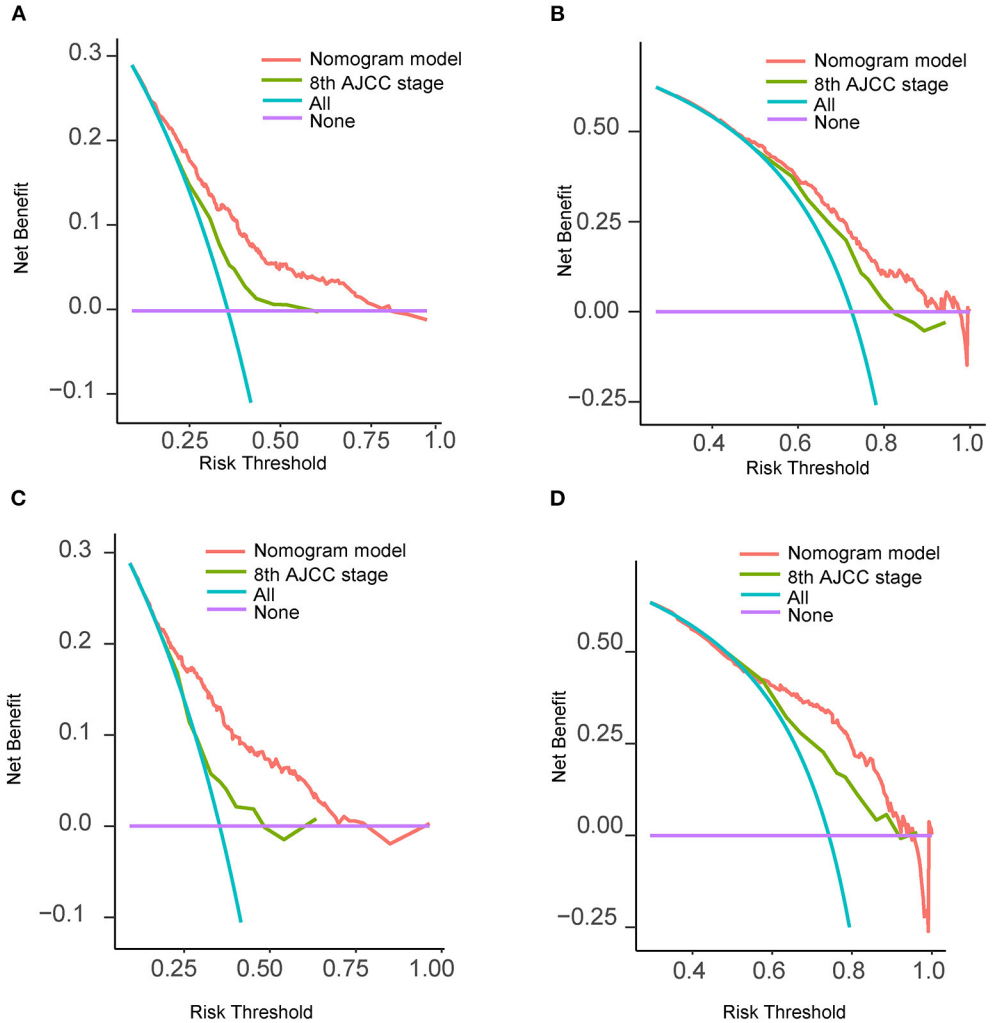

FIGURE 5 | Decision curves analysis and comparison of the nomogram with the 8th AJCC TNM staging system. **(A)** 1-year OS in the training cohort; **(B)** 3-year OS in the training cohort; **(C)** 1-year OS in the validation cohort; **(D)** 3-year OS in the validation cohort. AJCC, American Joint Committee on Cancer; OS, overall survival; TNM, tumor-node-metastasis.

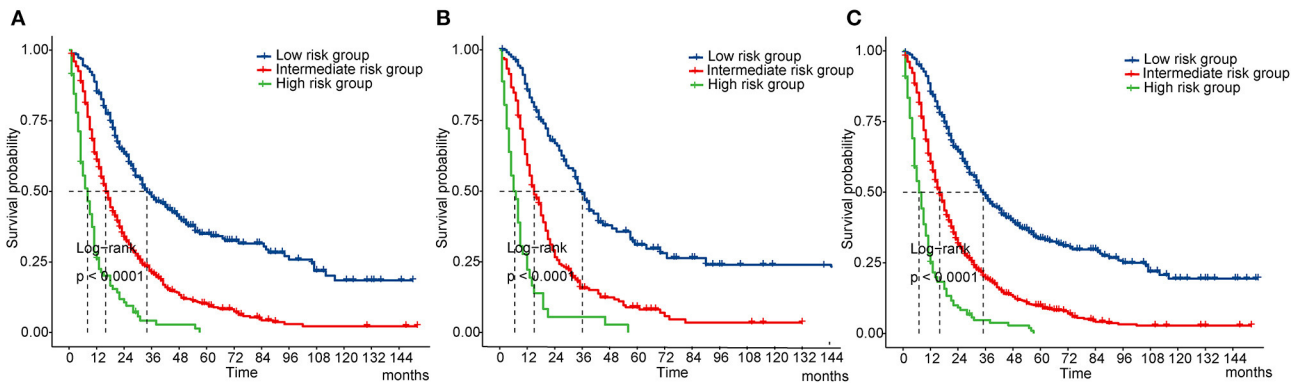

FIGURE 6 | Kaplan-Meier curves of OS for risk classification based on the nomogram scores. **(A)** In the training cohort; **(B)** In the validation cohort; **(C)** In all cohort. OS, overall survival.

almost single-centered and limited by their small sample sizes. Using data form SEER, a population-based, multi-centered and well-validated data set, the present study compared the long-term survival of PDAC patients following TP and PD. Patients with distant metastasis were excluded to remove the effects of tumor metastasis to survival. The PSM method was taken into use to minimize possible confounding effects and create well-matched cohorts. Before PSM, the results showed that OS and CSS in the unmatched TP and PD cohorts were similar. After PSM, no statistical differences in OS and CSS between the two cohorts were found. Improvement of survival in PDAC patients treated with TP may partly be due to the development of synthetic insulin, pancreatic enzyme supplementation, good glycemic control, education and self-management, which offer patients a stable postoperative metabolic status (29, 31). Therefore, the non-inferior long-term survival compared with PD may justify the use of TP for the treatment of PDAC in specific situations to achieve a complete resection, such as multifocal tumors and tumors with positive neck margins (32).

The nomogram, a simple statistical tool, has been well-recognized and widely used for prognosis prediction in which intricate mathematical models are converted to straightforward graphics (23, 33). Additionally, the nomogram can integrate various characteristics to give a more comprehensive and accurate prediction. Moreover, it can offer individualized prognosis predictions based on the characteristics of a given individual. Several studies have focused on survival prediction for patients with PDAC (34–36), but none have focus on those who are treated with TP. As mentioned above, TP can be safely performed with acceptable perioperative morbidity and mortality, and improved postoperative QoL and long-term survival. TP seems to be experiencing a renaissance in recent years; hence, it is helpful to develop a credible nomogram specifically for PDAC patients treated with TP.

Through univariate and multivariate Cox analysis, we found that age, AJCC T stage, differentiation, radiotherapy, chemotherapy and LNR were factors that significantly affected OS of the patients. Using X-tile, we obtained the optimal cutoff values of the continuous variables. Tumor characteristics were deemed to be important factors that could influence survival after pancreatic resection (37). In our model, AJCC T stage had the greatest impact on OS. The 8th AJCC system defines T4 stage as the pancreatic tumor has invaded the celiac axis, common hepatic artery, or superior mesenteric artery, which obviously leads to a poor prognosis. Tumor differentiation and age were also significantly associated with clinical outcomes, which is in agreement with previous studies (35, 36). Adjuvant chemotherapy is one element of comprehensive treatment for PDAC and is recommended in all patients (38), while radiotherapy or chemo-radiotherapy, especially in R1 resection, can be considered to improve OS of the patients (39). Our model verified that chemotherapy and radiotherapy could serve as protective factors for the patients, which proved the importance of multidisciplinary therapy (MDT) in the treatment of PDAC. The correlation between AJCC N stage and survival of the patients is controversial (40), since lymph node dissection may sometimes be insufficient. As Huebner et al. (40) reported in their study, in "N0" patients who had <11 examined lymph nodes after pancreatectomy, there was a probability that the metastatic lymph nodes were missed by harvesting too few nodes, and those patients generally had worse prognosis. We can see that under this circumstance, although the patients were judged as a favorable pathologically "N0" status, the survival turned out to be bad, which hints that *N* stage may not accurately predict survival sometimes, especially when fewer lymph nodes are moved from the patients. Riediger et al. (41) also reported that not the number of examined lymph nodes but LNR, was proved to be an independent prognostic factors after pancreas cancer resection. In this study, N stage turned out not to be a predictor in the model, whereas LNR was taken into account instead. LNR contains information on both the number of positive nodes and the total number of nodes evaluated, and increased LNR may better indicate the tendency of metastasis, as was reported in a previous study (35).

This nomogram relied on a cohort with a large sample size, which guaranteed the reliability of the results. The C-index were 0.67 (95% CI: 0.66–0.68) in the raining cohort and 0.69 (95% CI: 0.68–0.71) in the validation cohort, and calibration plots showed satisfactory consistency between the predicted and actual situations, which validated good discriminative capacity and predictive accuracy of the model. At present, the AJCC TNM system has been widely applied in clinical practice to predict the prognosis of cancer patients. However, the TNM system merely refers to the three anatomical elements of cancer but ignores other potential prognostic elements. Compared with the traditional system, our nomogram integrated more variables and demonstrated a better predictive effect. DCA puts benefit and harm together to calculate the net benefit of a prediction model, which takes clinical usefulness into consideration (25). Clinical usefulness weighs whether a prediction model can be reasonably used in clinical work, and patients can benefit from the model. In this study, the DCA curves further proved that our nomogram is superior to the TNM system with regard to clinical usefulness. Finally, based on the cutoff values of the nomogram overall scores, we formulated a risk stratification system, which could clearly differentiate patients with different survival risks.

For patients with PDAC following TP, what they concern most may be their postoperative QoL and survival time. This study successfully developed a nomogram to forecast prognosis according to the patients' clinicopathological information that could be easily obtained. Our nomogram provided a more individualized and precise prognosis prediction than the traditional AJCC staging system.

The present study had several limitations that need to be noticed. First, the study design was retrospective, which could lead to potential selection bias. Second, the SEER database lacks some important information, such as smoking and drinking status, serum CA19-9 level, surgical margin status, neurovascular invasion, detailed regimen and dosage of chemotherapy or radiotherapy, postoperative usage of insulin and pancreatic enzymes; hence we could not consider all potential prognostic factors. Third, although PSM was performed, there stilled existed some unobserved confounders, such as those mentioned above, which might affect the reliability of the results. Finally, although

the nomogram and its risk classification system had been internally validated with good performance, external validation support from other independent databases or populations is still needed to further assess the model.

CONCLUSIONS

In summary, for PDAC patients following TP, OS and CSS are similar to those who following PD. TP may be a reasonable option for PDAC patients if needed. Additionally, we developed a reliable and practical nomogram specifically for predicting the 1-, 3-, and 5-year OS of PDAC patients treated with TP, which showed superiority over the conventional AJCC staging system. This user-friendly nomogram could help clinicians make personalized survival predictions and risk assessments. Further prospective studies with more detailed clinical information and data from other large-scale cohorts are needed to improve and externally validate our model.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WS and JS: conception and design. ZL and JX: collection and assembly of data. XS, TT, and CX: data analysis and interpretation. WS: paper writing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.804785/full#supplementary-material

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Recurrence and Prognostic Value of Circulating Tumor Cells in Resectable Pancreatic Head Cancer: A Single Center Retrospective Study

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Background and Aim: To investigate the effect of preoperative circulation tumor cells (CTCs) on postoperative recurrence and overall survival prognosis of pancreatic head cancer after pancreaticoduodenectomy (PD).

Methods: From March 2014 to January 2018, 73 patients with pancreatic head cancer underwent radical resection (R0) in Zhongshan People's Hospital. CTCs in peripheral blood of patients with pancreatic head cancer were detected by "Cyttel" method before PD. Seventy-three patients were divided into positive and negative groups according to the positive criteria. To explore the relationship between the clinical data of CTCs and disease-free survival (DFS) and overall survival (OS). Cox proportional hazards model was used to analyzing the risk factors affecting the postoperative recurrence and the survival prognosis of patients.

Results: 41 patients (56.2%) were in the CTC-positive group. Preoperative CTCs were correlated with tumor vascular invasion, CA199 level and postoperative liver metastasis ($P < 0.05$). Preoperative CTC-positive, lymph node metastasis, vascular invasion, and nerve invasion were independent risk factors for DFS ($P < 0.05$). Preoperative CTC-positive, tumor diameter > 2 cm and vascular invasion were independent risk factors for OS of patients ($P < 0.05$).

Conclusion: The detection of CTCs before PD is an important factor affecting the DFS and OS of pancreatic head cancer, which is significant in guiding clinical work.

Keywords: pancreatic cancer, pancreaticoduodenectomy, recurrence, prognosis, circulating tumor cells

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INTRODUCTION

Pancreatic cancer is a common malignant tumor in the digestive system, which progresses rapidly because of its inconspicuous early clinical symptoms and high malignancy. Most patients are in the advanced stage when patients present with symptoms, with an inferior prognosis (1, 2). To date, pancreaticoduodenectomy (PD) is the mainstay of achieving long-term survival in patients with pancreatic head cancer (3–5). However, postoperative recurrence is a risk factor affecting the

prognosis of patients, and the 5-year survival rate varies between 5 and 20% (2, 5, 6). Therefore, it is of great significance to predict the postoperative recurrence of pancreatic head cancer to improve the survival prognosis of patients. Past studies have shown that tumor size, lymph node metastasis, vascular invasion, nerve invasion, and the level of CA199 are independent risk factors for postoperative recurrence and survival prognosis of pancreatic head cancer (7–10). In addition, CTCs play an essential role in the progression of malignant tumors. Many literatures have shown that CTCs are associated with OS and DFS of many malignant tumors, especially breast cancer, colorectal cancer, and prostate cancer (11–14). Therefore, this study explore the correlation between CTCs in postoperative recurrence and pancreatic head cancer survival prognosis.

MATERIALS AND METHODS

Patient Population

This study enrolled patients with pancreatic head cancer admitted to the Department of General Surgery I of Zhongshan People's Hospital from March 2014 to January 2018 and underwent PD treatment. Inclusion criteria (1) postoperative pathological diagnosis of pancreatic cancer; (2) detection of CTCs within 3 days before surgery; (3) no any neoadjuvant therapy; (4) radical resection (R0); (5) postoperative unified standard adjuvant chemotherapy; (6) with complete serological and imaging data; exclusion criteria: (1) patients younger than 18 years old; (2) the presence of adjacent organ invasion and distant metastasis; (3) patients died because of surgical complications during the perioperative period; (4) postoperative follow-up data were missing. This study was a retrospective clinical study reviewed by the Ethics Committee of Zhongshan People's Hospital and followed the Declaration of Helsinki.

Data Collection

All patients underwent abdominal enhanced Computed tomography (CT) or Nuclear magnetic resonance imaging (MRI), chest CT or X-ray scan. Laboratory tests include blood routine, liver and kidney function, coagulation function, CA199, and other examinations. Patients basic data, such as gender, age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatinine (Cr), blood urea nitrogen (BUN), albumin (Alb), total bilirubin (TIBL), direct bilirubin (DIBL), international normalized ratio (INR), thrombin time (PT), maximum tumor diameter, and pathological grade, were collected.

Abbreviations: PD, Pancreaticoduodenectomy; CT, Computed tomography; MRI, Nuclear magnetic resonance imaging; CTC, Circulating tumor cells; PT, Prothrombin time; INR, International normalized ratio; FIB, Fibrinogen; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase; Alb, Albumin; TIBL, Total bilirubin; DIBL, Direct bilirubin; BUN, Urea nitrogen; Cr, Creatinine; HR, Hazard ratio; SD, Standard deviation; IQR, Interquartile range; OS, Overall survival; DFS, Disease-free survival; EMT, Epithelial-mesenchymal transition.

Surgical Resection

Seventy-three patients with pancreatic cancer underwent surgical treatment at our medical center, and an experienced surgical team did all processes. The surgical methods were based on preoperative imaging examination and intraoperative exploration, including open pancreaticoduodenectomy (OPD) in 51 patients (69.9%), laparoscopic pancreaticoduodenectomy (LPD) in 20 patients (27.4%), and open pylorus-preserving pancreaticoduodenectomy in 2 patients (2.7%). Among the 21 patients of vascular invasion, 17 patients underwent surgical resection and direct vascular anastomosis, and 4 patients underwent surgical resection and vascular reconstruction to ensure that the surgical margin was R0 resection. R0 resection was defined as the absence of residual tumor tissue of 1 mm within the resection margin of the surgical specimen macroscopically and microscopically.

Analysis and Identification Methods of CTCs

Three days before surgery, we drew 5 ml of peripheral blood as a sample for inspection and strictly processed the sample according to the manufacturer's instructions. The "Cyttel" method (Jiangsu, China) identified the detection of CTCs, whose principles include negative immunomagnetic particle method and immunofluorescence *in situ* hybridization (im-FISH).

The former mainly uses immunomagnetic particles as the carrier, through the principle of antigen–antibody reaction, combined with centrifugation technology, to remove leukocytes from the blood *in vitro* to separate rare cells. Then, the samples were fixed on glass slides, dehydrated with ethanol, dried, and then hybridized with chromosome centromere probe No. 1 and chromosome centromere probe No. 8. Finally, 4-diamidine-2-phenylindole (DAPI) staining was added to seal the samples, and the CTCs were observed and counted under a fluorescence microscope (15, 16). It defined CTC count $\geq$1 as CTC-positive.

Follow-Up

All patients were followed up throughout-patient service, telephone or WeChat. Follow up examination items included chest X-ray or chest CT scan, abdominal ultrasound, abdominal enhanced CT or MRI and PET-CT. They were followed up every 3 months for 2 years after surgery, from the day of surgery, and every 6 months after 2 years after surgery. Overall survival (OS) was defined as the time from surgery to patient death or last follow-up, and disease-free survival (DFS) was defined as the time from surgery to postoperative tumor recurrence or last follow-up. The cut-off date was July 1, 2021.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD), if they met normal distribution and had equal variance; the student's *t*-test was used to compare two groups. Continuous variables not meeting normal distribution and had equal variance were expressed as [median, interquartile range (IQR)], Kruskal-Wallis test was used for comparison between two groups; Categorical variables were reported as number (n) or percentages of patients (%). The $\chi 2$ test or Fisher's exact test

compared categorical variables; Cox proportional hazards model was used for univariate and multivariate analysis; Kaplan-Meier method was used to measure DFS curve and OS curve. Log-rank test was used to compare DFS and OS between two groups; $P < 0.05$ was considered statistically significant. The above statistical analysis uses the R language (version 3.62). The main R package used is "tableone," "survival" and "survminer" packages.

RESULTS

Baseline Characteristics

This study collected 90 patients with pancreatic head cancer who underwent PD, and 73 patients (81.1%) underwent R0 resection. In the overall study population, 38 were male and 35 were female. The age range was 36–80 years, with a mean age of 62 years. The tumor diameter was between 1.2 and 5.0 cm, the mean tumor maximum diameter was 2.3 cm, 46 patients (63.0%) had tumors >2 cm in maximum diameter, and 38 patients (52.1%) had CA199 > 37 U/L. Lymph node metastasis was found in 38 patients (52.1%), vascular invasion in 21 patients (28.8%), and nerve invasion in 36 patients (49.3%). The clinicopathological data of the patients is shown in **Supplementary Table 1**.

Relationship Between CTCs in Peripheral Blood and Clinical Data in Patients With Pancreatic Head Cancer

Peripheral blood CTCs were positive in 41 of 73 patients with pancreatic head cancer, ranging from 0 to 6 cells/3 mL, and preoperative CTCs positivity was significantly correlated with vascular invasion and preoperative CA199 ($P < 0.05$, **Table 1**). There was no statistical significance with clinical data such as gender, age, pathological grade, tumor size, lymph node metastasis, Cr, BUN, ALT, AST, Alb, TBIL, and DIBL ($P > 0.05$, **Table 1**). This suggests that preoperative CTCs are associated with tumor progression.

Postoperative Recurrence of Pancreatic Head Cancer

All patients were followed up for an average of 14.8 months, ranging from 2 to 36 months. Fifty-nine patients had a recurrence, with a postoperative recurrence rate of 80.8% (59/73), most of which had recurrence at 1 year, with a recurrence rate of 65.8% (48/73) within 1 year. There were 17 patients of retroperitoneal recurrence alone and 40 patients of retroperitoneal recurrence with distant metastasis, including 24 patients of liver metastasis, 12 patients of peritoneal spread, 2 patients of pulmonary metastasis, 2 patients of spinal metastasis. In addition, 2 patients had liver metastases alone.

Relationship Between CTCs and Postoperative Liver Metastasis

The mean CTCs was 2.7 in 26 patients with liver metastasis, 0.7 in the retroperitoneal metastasis group, and 1.0 in the retroperitoneal and peritoneal spread group after the operation.

TABLE 1 | Relationship between preoperative CTCs and basic clinicopathological characteristics of patients with pancreatic head cancer.

Variable	CTC-negative ($n = 32$)	CTC-positive ($n = 41$)	*P*
Gender (%)			0.308
Male	14.00 (43.75)	24.00 (58.54)	
Female	18.00 (56.25)	17.00 (41.46)	
Age (years mean[SD])	59.97 (9.12)	63.68 (7.91)	0.067
CA199 (U/L median [IQR])	19.45 [11.20, 44.70]	96.20 [8.40, 573.28]	< 0.05
PT (s median [IQR])	11.45 [10.97, 11.90]	11.70 [11.30, 12.10]	0.247
INR (median [IQR])	1.00 [0.93, 1.05]	1.02 [0.97, 1.06]	0.245
FIB (g/L median [IQR])	3.25 [2.77, 4.38]	3.59 [3.10, 4.21]	0.685
ALT (U/L median [IQR])	44.00 [12.75, 109.28]	71.00 [20.00, 244.00]	0.061
AST (U/L median [IQR])	28.50 [17.50, 87.25]	65.00 [19.00, 143.00]	0.201
LDH (U/L median [IQR])	174.00 [144.00, 220.00]	185.00 [163.00, 232.00]	0.149
Alb (g/L median [IQR])	41.70 [37.00, 43.18]	41.30 [36.60, 43.70]	0.726
TIBL (umol/L median [IQR])	16.05 [10.10, 143.88]	91.30 [14.20, 199.80]	0.100
DIBL (umol/L median [IQR])	5.30 [3.80, 102.32]	44.60 [4.00, 145.20]	0.230
BUN (mmol/L median [IQR])	4.09 [3.39, 5.64]	4.20 [3.20, 5.40]	0.925
Cr (umol/L median [IQR])	61.50 [53.75, 80.25]	67.00 [55.00, 80.00]	0.697
Tumor diameter [cm mean (SD)]	2.18 (0.84)	2.47 (0.64)	0.096
Pathological grade (%)			0.203
Low	10.00 (31.25)	13.00 (31.71)	
Medium	7.00 (21.88)	16.00 (39.02)	
High	15.00 (46.88)	12.00 (29.27)	
Vascular infiltration (%)			<0.05
No	32.00 (100.00)	20.00 (48.78)	
Yes	0.00 (0.00)	21.00 (51.22)	
Nerve invasion (%)			0.122
No	20.00 (62.50)	17.00 (41.46)	
Yes	12.00 (37.50)	24.00 (58.54)	
Metastases to lymph nodes (%)			0.136
No	19.00 (59.38)	16.00 (39.02)	
Yes	13.00 (40.62)	25.00 (60.98)	

PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; Alb, albumin; TIBL, total bilirubin; DIBL, direct bilirubin; BUN, urea nitrogen; Cr, creatinine; CTC, circulating tumor cell; SD, standard deviation; IQR, interquartile range.

By Kruskal-Wallis test, the CTC in the group with liver metastasis was significantly higher than that in the retroperitoneal and peritoneal spread group ($P < 0.05$, **Figure 1**). There was no significant difference in the CTCs between the retroperitoneal and peritoneal spread groups ($P > 0.05$, **Figure 1**).

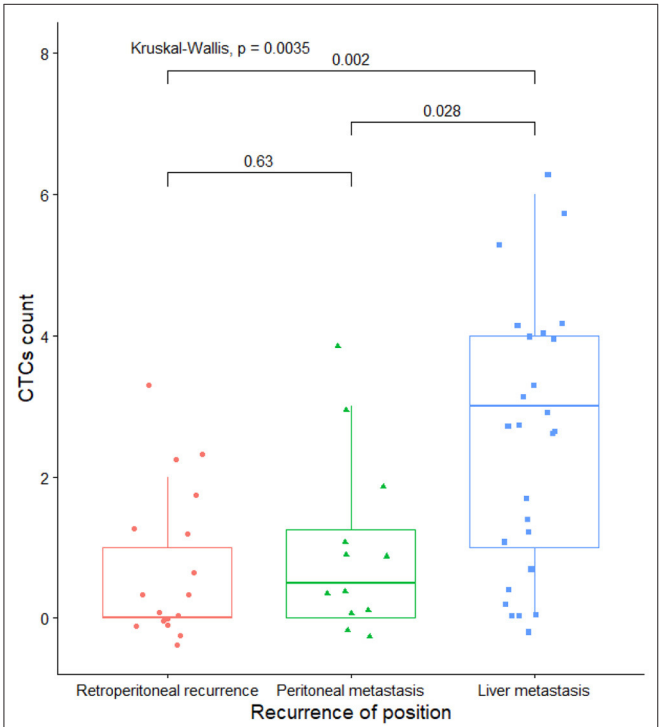

FIGURE 1 | Relationship between CTCs content and the site of postoperative recurrence.

Preoperative CTCs for Recurrence and Survival Prognosis of Patients With Pancreatic Head Cancer After Surgery

The median recurrence time was 5 months in patients with CTC-positive and 15 months in the CTC-negative group. The 1-year DFS rates were 59.2 and 7.8% in the CTC-negative and CTC-positive groups, respectively. The DFS of the CTC-positive group was significantly lower than that of the CTC-positive group. The difference was statistically significant ($P < 0.05$, **Figure 2A**). In terms of OS, the median survival time was 10 months and 25 months in the CTC-positive and CTC-negative group, respectively, and the 1-year survival rate was 87.5, 24.2% in the CTC-positive and CTC-negative group, respectively. The difference was statistically significant ($P < 0.05$, **Figure 2B**).

Analysis of Independent Risk Factors of Postoperative Recurrence and Survival Prognosis

Univariate Cox analysis showed that CTC-positive, tumor size, lymph node metastasis, vascular invasion, nerve invasion, and preoperative CA199 > 37 U/L were prognosis factors for DFS ($P < 0.05$, **Table 2**), and multivariate Cox analysis suggested that CTC- positive, lymph node metastasis, vascular invasion, and nerve invasion were independent prognosis factors for DFS ($P < 0.05$, **Table 2**).

We explored which clinicopathological data affected the OS of patients. Univariate Cox analysis showed that CTC-positive, tumor size, vascular invasion, nerve invasion, and preoperative CA199 > 37U/L were risk factors for OS, and multivariate Cox analysis suggested that CTC-positive, tumor size and vascular invasion were independent risk factors for OS ($P < 0.05$, **Table 3**).

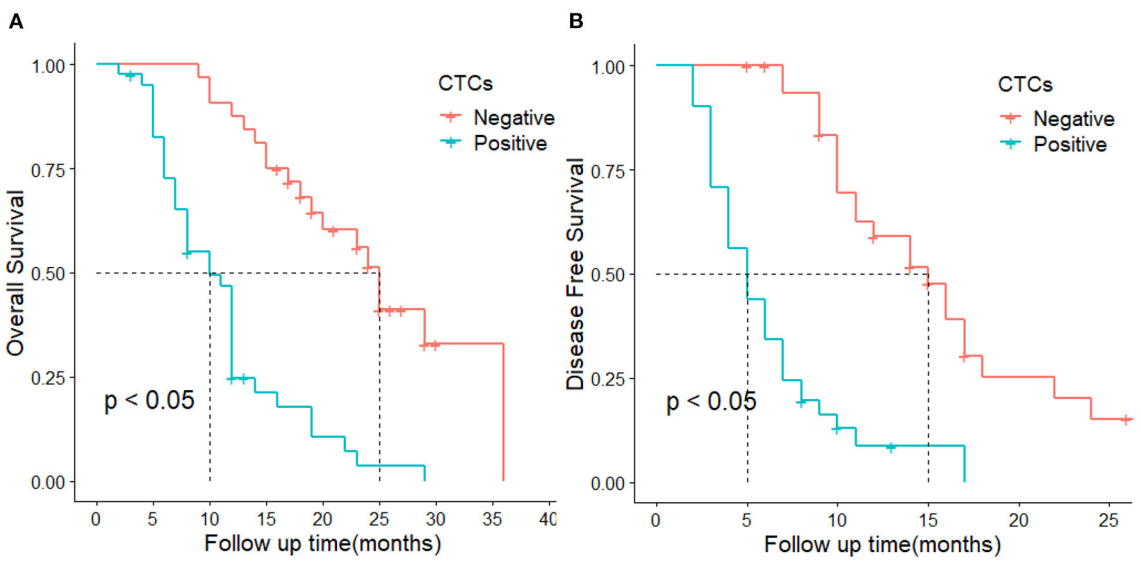

FIGURE 2 | DFS and OS in CTC-positive and negative groups. **(A)** represents overall survival, **(B)** represent disease-free survival.

TABLE 2 | Analysis of influencing factors of DFS of pancreatic head cancer.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Gender	0.676 (0.403–1.134)	>0.05		
Age	0.996 (0.967–1.026)	>0.05		
CA199 (>37 U/L)	1.890 (1.113–3.208)	<0.05	0.870 (0.466–1.626)	>0.05
PT	1.006 (0.924–1.095)	>0.05		
INR	1.092 (0.411–2.900)	>0.05		
FIB	1.098 (0.850–1.418)	>0.05		
ALT	1.000 (0.998–1.001)	>0.05		
AST	1.000 (0.998–1.002)	>0.05		
LDH	1.000 (0.996–1.005)	>0.05		
Alb	0.980 (0.924–1.038)	>0.05		
TIBL	1.001 (0.998–1.003)	>0.05		
DIBL	1.001 (0.998–1.004)	>0.05		
BUN	1.020 (0.992–1.049)	>0.05		
Cr	0.997 (0.983–1.010)	>0.05		
Tumor diameter >2 cm	2.668 (1.507–4.723)	<0.05	0.934 (0.446–1.955)	>0.05
CTC-positive	5.799 (3.158–10.649)	<0.05	4.172 (2.000–8.704)	<0.05
Low differentiation	1.123 (0.602–2.096)	>0.05		
Vascular invasion	6.931 (3.626–13.247)	<0.05	4.452 (1.934–10.244)	<0.05
Nerve invasion	2.212 (1.310–3.735)	<0.05	2.071 (1.073–3.996)	<0.05
Metastases to lymph nodes	1.951 (1.157–3.291)	<0.05	2.775 (1.563–4.928)	<0.05

PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; Alb, albumin; TIBL, total bilirubin; DIBL, direct bilirubin; BUN, urea nitrogen; Cr, creatinine; CTC, circulating tumor cell; HR, hazard ratio.

DISCUSSION

Previous studies have shown that CTCs are tumor cells immersed in peripheral blood by malignant tumors as epithelial-mesenchymal transition (EMT). The immune system will recognize and remove most CTCs through cellular and humoral immunity, but a few CTCs can masquerade as normal cells to avoid immune surveillance and realize immune escape.

Tumor cells not monitored by the immune system play a vital role in the implantation, dissemination, and distant metastasis of malignant tumors by migration, adhesion, and other means, and are even closely related to the postoperative recurrence or even survival prognosis of patients (17, 18).

In recent years, some researches have gradually applied the detection of CTCs as a liquid biopsy technique to the study of postoperative recurrence and the survival prognosis of pancreatic cancer. Unfortunately, some studies have failed to achieve meaningful results, mainly due to: (1) Pancreatic cancer differs from other malignant tumors, with more interstitial components, relatively low tumor burden, and correspondingly fewer tumor cells flowing into the peripheral blood; (2) The venous return of the pancreas is not directly drained into the inferior vena cava to converge in the liver through the hepatic portal system; thus, this is also the reason the distant metastasis of pancreatic cancer is more likely to occur in the liver (19–23). Domestic and foreign studies have also shown that CTCs are related to pancreatic cancer invasion, and ultimately affect the postoperative recurrence and survival prognosis of pancreatic cancer (24, 25). Based on the debate, we used the "Cyttel" method to detect CTCs to explore their relationship with clinical features and the impact of postoperative recurrence and survival prognosis.

In the present study, the positive rate of preoperative CTCs in pancreatic head cancer was 56.1%, and the positive rate was roughly comparable with that reported in the past using nano microfluidic chip technology to detect CTCs in pancreatic cancer (24). But, it is lower than 64–73% of other gastrointestinal digestive malignancies (26). In order to solve the problem of the low detection rate of CTCs in pancreatic cancer caused by the return of pancreatic veins to the liver through the portal venous system, Wang et al. tried to directly extract portal vein blood to improve the detection rate of CTCs (27). Unfortunately, the detection rate of CTCs has not been effectively improved, and they believe that this is related to the lack of professional collection equipment and reagents for preserving samples, which also provides a lot of inspiration for our future research. In addition, Our research also found that the positive rate of peripheral blood CTCs detection in patients with postoperative liver metastasis was higher than that in patients with retroperitoneal local recurrence or peritoneal spread, and it was statistically significant. The results of this study have never been reported in past studies. Domestic scholar Liu's team carried out a relevant study on portal vein CTCs and liver metastasis of pancreatic cancer and found that it correlated

TABLE 3 | Analysis of prognostic factors of postoperative survival of pancreatic head cancer.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Gender	0.826 (0.479–1.422)	>0.05		
Age	1.014 (0.981–1.047)	>0.05		
CA199 >37 U/L	2.568 (1.446–4.498)	<0.05	1.159 (0.588–2.283)	>0.05
PT	1.027 (0.948–1.113)	>0.05		
INR	1.376 (0.556–3.408)	>0.05		
FIB	1.159 (0.905–1.483)	>0.05		
ALT	1.001 (0.997–1.003)	>0.05		
AST	1.002 (1.000–1.004)	>0.05		
LDH	1.002 (0.997–1.007)	>0.05		
Alb	0.992 (0.935–1.052)	>0.05		
TIBL	1.002 (0.999–1.004)	>0.05		
DIBL	1.002 (0.999–1.005)	>0.05		
BUN	1.022 (0.996–1.049)	>0.05		
Cr	1.004 (0.991–1.018)	>0.05		
Tumor diameter >2cm	7.897 (3.737–16.691)	<0.05	4.077 (1.760–9.443)	<0.05
CTC-positive	5.290 (2.864–9.773)	<0.05	2.463 (1.180–5.139)	<0.05
Low differentiation	1.344 (0.691–2.611)	>0.05		
Vascular invasion	7.450 (3.984–13.930)	<0.05	2.421 (1.103–5.316)	<0.05
Nerve invasion	2.236 (1.289–3.880)	<0.05	1.478 (0.826–2.645)	>0.05
Metastases to lymph nodes	1.700 (0.970–2.981)	>0.05		

PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; Alb, albumin; TIBL, total bilirubin; DIBL, direct bilirubin; BUN, urea nitrogen; Cr, creatinine; CTC, circulating tumor cell; HR, hazard ratio.

portal vein CTCs with liver metastasis (28). Although the CTCs shed from the primary lesion pass through the filtering effect of the liver, a considerable number of CTCs can still reach the peripheral blood circulation. We can indirectly know the portal vein CTCs load by detecting peripheral blood CTCs, to predict the probability of postoperative liver metastasis better. The timely and effective removal or intervention of these so-called "metastases" of CTCs ultimately achieves the purpose of improving the postoperative survival of pancreatic cancer. The detection of CTCs from peripheral blood has great advantages over the detection of portal vein CTCs, which are manifested in: (1) the technique of obtaining CTCs from peripheral blood is easier to operate, the technical threshold is lower, and there is no need for the support of ultrasound, CT and other related equipment; (2) The operation of collecting CTCs through the portal vein is perilous. If there is a mistake in collecting portal blood, it may lead to the rupture of the portal vein and even endanger the patient's life. In summary, we believe CTC-positive associate with postoperative recurrence. The detection of CTCs in peripheral blood provides a brand-new indicator for clinical decision-making and has certain clinical value.

Firstly, considering that patients with CTC-positive are prone to recurrence after surgery, can we perform neo-adjuvant therapy in this part of patients to eliminate occult lesions in order to improve the DFS and OS (29). Secondly, the detection of CTCs in peripheral blood is helpful for the early detection of postoperative liver metastases. By strengthening postoperative monitoring of CTCs-positive patients, early detection of liver metastases and timely intervention of liver metastases (surgical resection or radiofrequency ablation) can be achieved, and to improve the long-term survival of patients (30).

Finally, our study also found that CTC-positive was correlated with vascular invasion, the concentration of high level of CA199, and not with clinicopathological variables such as age, tumor size, lymph node metastasis, nerve invasion, or pathological grade, which were the same as those reported in the past literature (24, 25, 31); As for the relationship with the preoperative CA199 level, a few scholars have reported (32). Of course, this needs to be confirmed by more studies in the future.

Our study also analyzed the clinicopathological variables associated with DFS and OS of patients using univariate and multivariate Cox proportional hazards models. CTC-positive, vascular invasion, nerve invasion, and lymph node metastasis are independent risk factors for postoperative recurrence, and the latter three variables have also been confirmed in past studies (33–38). CTC-positive, vascular invasion, and tumor size were independent risk factors affecting OS, which were also consistent with past reports (39, 40). The above results show that peripheral blood CTCs play a pivotal role in DFS and OS in patients with pancreatic cancer.

Of course, our study also has limitations: (1) The size of our study population is small, and we expect a larger population to verify our conclusions in the future; (2) Considering the high cost of CTCs detection, it cannot be used as a routine

detection method, especially in economically backward areas. But we believe that with the improvement of detection methods, the cost of CTCs detection will be reduced. It will be more commonly used in clinical work.

CONCLUSION

In conclusion, we believe the CTCs are related to the postoperative recurrence and survival prognosis of pancreatic head cancer, and can be used as an important indicator to evaluate the recurrence risk and clinical prognosis of pancreatic head cancer. We believe that the detection of CTCs will help to guide the clinical practice of pancreatic head cancer in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

QZ and FX wrote the manuscript. AM and QS provided the cases. AM, JC, and WZ provided the nuclear medical images and interpretation of the data. WCa provided data. WCh reviewed and edited the manuscript. All authors read and approved the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.832125/full#supplementary-material

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Risk Factors and Clinical Impacts of Post-Pancreatectomy Acute Pancreatitis After Pancreaticoduodenectomy: A Single-Center Retrospective Analysis of 298 Patients Based on the ISGPS Definition and Grading System

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Background: The definition and grading system of post-pancreatectomy acute pancreatitis (PPAP) has recently been proposed by ISGPS. This study aimed to put this definition and classification into practice and investigate the potential risk factors and clinical impacts of PPAP.

Methods: Demographic and perioperative data of consecutive patients who underwent pancreaticoduodenectomy (PD) from January 2019 to July 2021 were collected and analyzed retrospectively. The diagnostic criteria of PPAP published by ISGPS, consisting of biochemical, radiologic, and clinical parameters, were adopted. The risk factors were analyzed by univariate and multivariate analyses.

Results: A total of 298 patients were enrolled in this study, and the total incidence of PPAP was 52.4% (150 patients). Stratified by clinical impacts of PPAP, the incidences of grades B and C PPAP were 48.9% and 3.5%, respectively. PPAP after PD was significantly associated with pancreatic fistula and other unfavorable complications. Soft pancreatic texture (OR 3.0) and CRP ≥ 180 mg/L (OR 3.6) were the independent predictors of PPAP, AUC 0.613. Stratified by the grade of PPAP, soft pancreatic texture (OR 2.7) and CRP ≥ 180 mg/L (OR 3.4) were the independent predictors of grade B PPAP, and soft pancreatic texture (OR 19.3), operation duration >360 min (OR 13.8), and the pancreatic anastomosis by using conventional duct to mucosa methods (OR 10.4) were the independent predictors of grade C PPAP. PPAP complicated with pancreatic fistula significantly increased the severe complications and mortality compared to only PPAP occurrence.

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Conclusion: PPAP was not an uncommon complication after PD and was associated with unfavorable clinical outcomes, especially since it was complicated with pancreatic fistula. Soft pancreatic texture and CRP ≥ 180 mg/L were the independent predictors of PPAP. Higher-volume multicenter and prospective studies are strongly needed.

Keywords: pancreaticoduodenectomy, acute pancreatitis, postoperative complications, risk factors, retrospective analysis

INTRODUCTION

Post-ERCP pancreatitis (PEP) has been widely recognized, and its clinical practice guidelines have been published (1). Under the same postoperative background, postpancreatectomy acute pancreatitis (PPAP) was not comprehensively recognized. Previous studies regarded PPAP as an indirect manifestation of pancreatic fistula (PF) (2, 3). PPAP has attracted attention since Connor proposed the first definition based on the systematic review (4). Several medical centers carried out their clinical studies relevant to PPAP (5–9), and the incidence reported in previous studies varied widely from 1.5% to 67.9% due to the lack of authoritative definitions and terminology.

Recently, the international study group of pancreatic surgeons (ISGPS) developed a consensus definition, diagnostic, and grading criterion of PPAP. PPAP is defined as acute inflammation of the remnant pancreas within the first 3 days after partial pancreatectomy. The ISGPS group come up with the term "PPAP" instead of postoperative pancreatitis (POAP) (4) to refer specifically to pancreatitis after partial pancreatectomy. This group also clarified the definition of postoperative serum hyperamylasemia (POH), which had previously been confused with PPAP (10). The diagnostic criteria of PPAP (11) require three dimensions: sustained POH, clinical impacts relevant to PPAP, and radiologic features of acute pancreatitis (12, 13). The grading system of PPAP is based on clinical impacts, including POH (biochemical change only), grade B (mild or moderate clinical impacts), and grade C (severe clinical impacts).

Here, in this study, we used the definition and grading system of PPAP that had just been published by ISGPS to review our clinical data and aimed to assess PPAP in our clinical practice and recognize potential risk factors of PPAP.

METHODS

Patients and Data Collection

This retrospective study was performed on all patients who consecutively underwent pancreaticoduodenectomy (PD) from January 2019 to July 2021 at the First affiliated Hospital of Xi'an Jiaotong University. Patients who got a PD procedure in the Department of Hepatobiliary Surgery were enrolled in this study. Patients without a detailed record of postoperative complications, serum amylase, and abdominal CT scan in the early postoperative period were excluded. This study was approved by the local ethics committee (ethical approval number: XJTU1AF2015LSL-057), and informed consent was obtained from the patients.

To control bias, demographics, preoperative clinical parameters, and postoperative clinical parameters were collected by different individuals to reduce the behavior of artificial adjustment and the influence of personal tendency in the data collection phase. Demographic characteristics included age, gender, body mass index (BMI), smoking, and drinking conditions. Past medical history and comorbidities included cardiovascular and pulmonary diseases, hepatitis, kidney diseases, cholelithiasis, type 2 diabetes mellitus, history of acute pancreatitis attack and previous abdominal surgery, preoperative jaundice, and the American Society of Anaesthesiologists (ASA) score.

Operative details included blood loss, transfusion, and operative duration. The surgical procedure details also contained whether pylorus-preserving pancreaticoduodenectomy (PPPD) (14) or Whipple procedure (15), standard or extended resection (vascular resection and/or extended organ resection), the usage of pancreatic duct stent, and the diameter of the pancreatic duct. The pancreatic texture was assessed by the primary surgeon and documented in the surgical records. The fistula risk scores (16) were calculated. The management of pancreatic stump in operations was all treated with pancreatojejunostomy (PJ), none of the pancreatogastric anastomosis (PG), including modified Blumgart pancreatic duct–mucous anastomosis, double-layer duct-to-mucosa (conventional duct to the mucosa), and end-to-side or end-to-end invagination. Pathology types were divided into three groups: the first was pancreatic ductal adenocarcinoma (PDAC) and chronic pancreatitis (CP), the second was another malignant group (periampullary carcinoma, duodenal carcinoma), and the third was the benign and low malignant group (pancreatic cyst tumor, pancreatic neuroendocrine tumor, duodenal stromal tumor, and other benign or precancerous lesions).

The removal time and volume of drainage tubes, including gastric, urine, and abdominal drainage tubes, were collected by the medical orders and medical records. The number of patients who accepted the neoadjuvant therapy was collected. The usage of the pancreatic exocrine inhibitory drug (octreotide or somatostatin) and ulinastatin was recorded. The length of hospital stay, postoperative hospital stay, intensive care unit (ICU) stay, postoperative mortality, and gross cost were collected. Perioperative serum biochemical markers including CRP (on POD 0–3), total bilirubin (TB), direct bilirubin, albumin (ALB), calcium, and amylase were also recorded.

Definitions

The preoperative jaundice state means serum TB ≥ 34.2 μmol/L (more than 2 times the upper normal serum level) before the surgery. The liquid intake/output volume was defined as the difference between all intake volume and output (urine volume plus blood loss) on the day of operation (POD 0) including intraoperative. About 2000 ml (roughly the physiological requirements) was the cutoff to assess the liquid intake/output volume. The measures of preoperative biliary drainage include percutaneous transhepatic biliary drainage (PTBD), endoscopic nasobiliary drainage (ENBD), and T-shaped tube placed in the previous operation. The volume of abdominal drainage, namely, extraintestinal drainage on the postoperative day, did not include the intestinal drainage such as the pancreatic duct stents, biliary stents, PTBD, and gastric tubes. Hypoalbuminemia was defined as the serum concentration on POD 1 of less than 3.5 g/dL (35 g/L), and serum calcium on POD 1 below the lower limit was defined as hypocalcemia. The ΔTB was equal to the postoperative minus preoperative TB value on POD 1. The unchanged ΔTB ranged from −5 μmol/ L to 5μmol/ L, higher than that defined as elevation and lower than that defined as decrease.

The definition and severity of PPAP (11), PF (17), delayed gastric empty (DGE) (18), and postpancreatectomy hemorrhage (PPH) (19) were according to ISGPS. Bile leakage (BL) was defined as the concentration of bilirubin in the drainage fluid >3 times of the serum bilirubin on or POD 3 or requiring radiological or surgical intervention due to biliary collection or biliary peritonitis (20). Intra-abdominal infection was supported by evidence of bacterial culture etiology in the abdominal drainage fluid. Wound infection was proved by purulent discharge or the need to remove the suture and drainage. Acute kidney injury (AKI) was according to the Kidney Disease Improving Global Outcomes (KDIGO) classification (21). The abdominal fluid collection was confirmed by imaging (ultrasound or CT scans). Percutaneous drainage was guided by ultrasound or CT scans under local infiltration anesthesia. Unplanned reoperation meant the unplanned need for laparotomy or interventional surgery during the hospital stay. The severity of complications was according to the Clavien–Dindo classification (22); the ≥IIIb complications were defined as serious complications. Postoperative mortality was stipulated as mortality within 30 days after surgery.

Evaluation of Postoperative CT

Postoperative CT scans were evaluated by the team of the Department of Radiology at the First Affiliated Hospital of Xi'an Jiaotong University, which consisted of one professor and two associate professors majoring in the abdominal area. This team reached a consensus on the manifestations of PPAP on postoperative CT images (**Figure 1**). Based on the radiological features in the early postoperative period (11, 12), PPAP can be stratified into acute edematous pancreatitis and acute necrotizing pancreatitis. Interstitial edematous pancreatitis shows relatively homogeneous enhancement or attenuation, inflammatory change, and peripancreatic fluid collection (**Figure 1A**), while acute necrotizing pancreatitis shows inhomogeneous enhancement or attenuation, necrosis of the pancreatic parenchyma and/or the peripancreatic tissue (**Figure 1B**).

Statistics

SPSS 21.0 software package was used for data processing. The normal distribution data are described by $\bar{x} \pm s$, the non-normal distribution data are described by median (IQR), and the counting data are described by proportion, relative ratio, and composition ratio. The Mann–Whitney *U* test for two

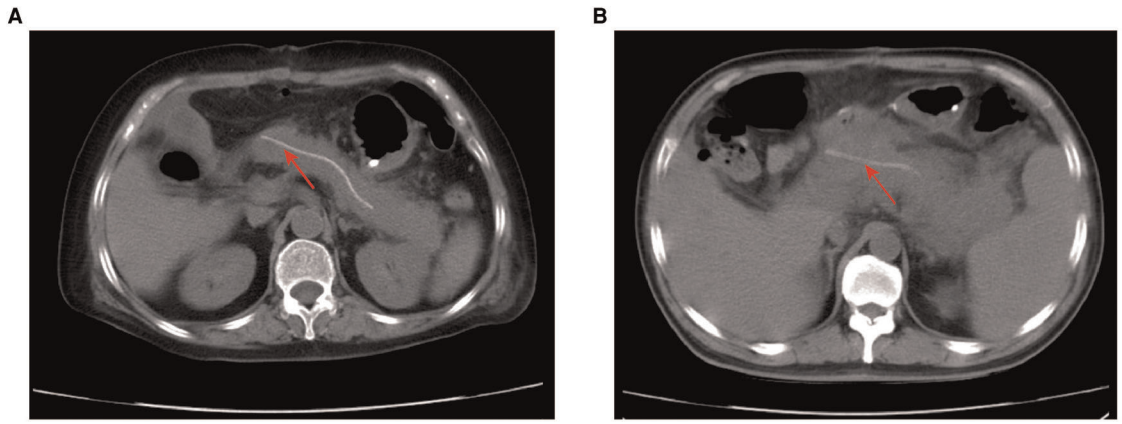

FIGURE 1 | Postoperative CT scans of PPAP. (**A**) Acute edematous pancreatitis after PD: the boundary of the remnant pancreas is coarse, extensive exudation and inflammatory change around the remnant pancreas, not the surgical field. (**B**). Acute necrotizing pancreatitis after PD: the borderline of remnant pancreas is not distinct, inflammatory changes and exudate surrounding the remnant pancreas, necrosis change in the pancreatic parenchyma and the peripancreatic tissue. Red arrow: internal pancreatic duct stent. PPAP, postoperative acute pancreatitis; PD, pancreaticoduodenectomy.

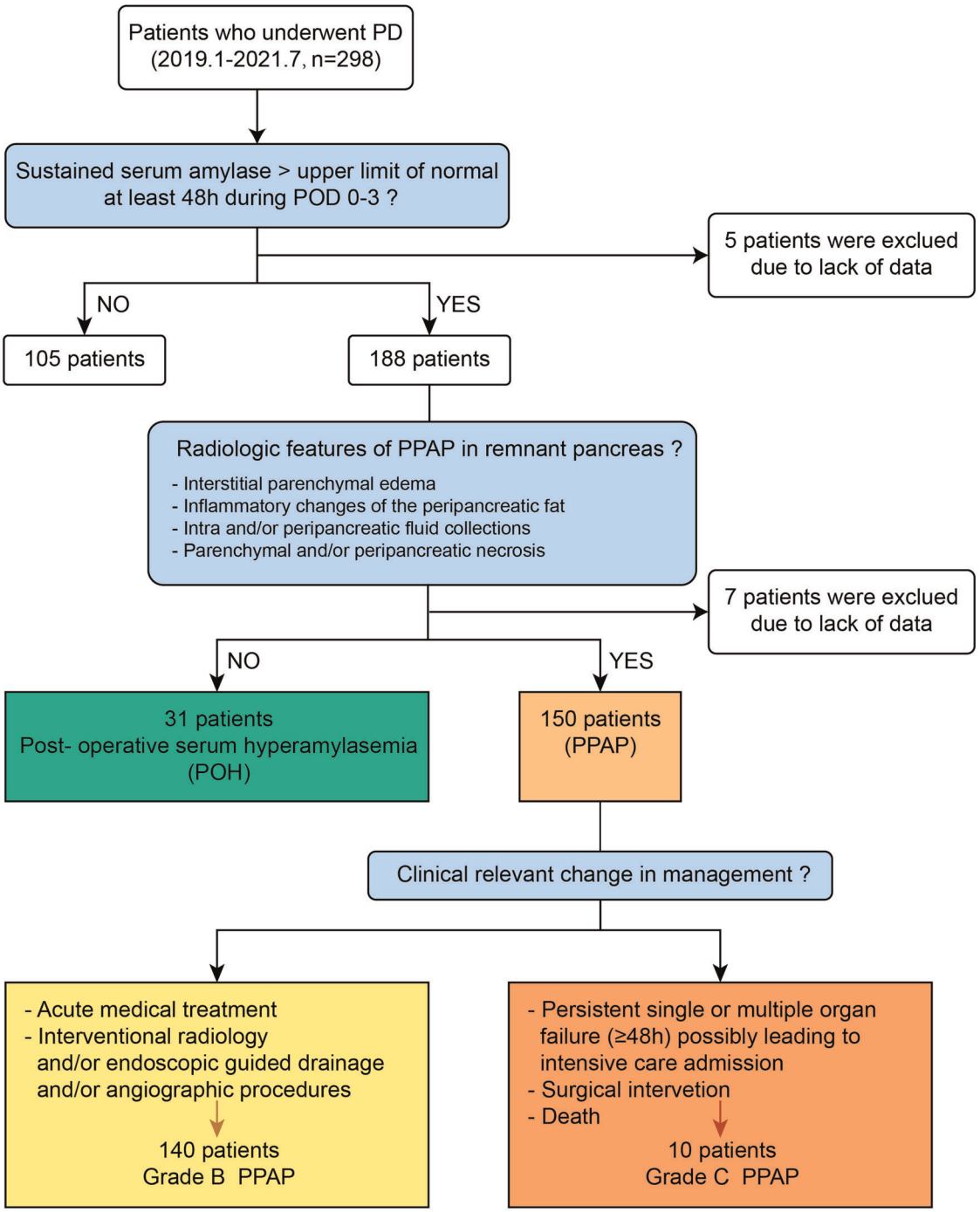

FIGURE 2 | Diagnostic flow chart of PPAP based on the diagnostic criteria of ISGPS.

independent samples was used for non-normal distribution. Pearson's chi-square test was used for counting data, and the *t*-test was used for two independent samples in accordance with normal distribution. Univariate analysis was used to judge the association between perioperative parameters and PPAP. Multivariate analyses, including binary and Firth logistic regression, were used to recognize the risk factors of PPAP and PF. The efficiency of the predicting model was measured by ROC curve analysis. *P* values <0.05 were defined as statistically significant.

RESULTS

Patients' Characteristics

A total of 298 consecutive patients who underwent PD from January 2019 to July 2021 at the First affiliated Hospital of Xi'an Jiaotong University were enrolled in this study. Twelve (4.0%) patients were excluded due to the lack of detailed records of postoperative complications, serum amylase, and abdominal CT scan data. The sex ratio of men to women was 1.6:1. The mean age of the patients was 62 (55–69) years. Twenty-three (8%) patients had a history of acute pancreatitis attack, and 71 (24.8%) had cholelithiasis. Sixty-two (21.7%) patients had abdominal surgery previously. The most frequent indications for PD were malignant tumors, including 92 (32.2%) pancreatic ductal adenocarcinoma, 157 (54.9%) periampullary carcinoma, and 6 (2.1%) duodenal carcinoma. The residual contains 16 (5.6%) pancreatic cyst tumor, 4 (1.4%) pancreatic neuroendocrine tumor, 3 (1.0%) chronic pancreatitis, 2 (0.7%) duodenal stromal tumor, and 6 (2.1%) other benign or precancerous lesions. According to diagnostic criteria of PPAP formulated by ISGPS, the patients were divided into the PPAP group and non-PPAP group (the diagnostic flow chart is shown in **Figure 2**); the total incidence of PPAP was 52.4% (150 patients). Stratified by clinical impacts of PPAP, grade B PPAP was 48.9% (140 patients) and grade C PPAP was 3.5% (10 patients). The serum amylase level on POD 1–3 is shown in Supplementary Table 1 (the normal upper limit of serum amylase in our institution is 135 U/L). The incidence of clinically relevant pancreatic fistula (CR-PF) was 23.4% (67 patients). Of the patients with CR-PF, 56 (19.6%) patients had grade B PF and 11 (3.8%) patients had grade C PF.

PPAP After PD Was Associated with Unfavorable Complications

The postoperative outcomes of patients grouped by the occurrence of PPAP are shown in **Table 1**. The complications of Clavien–Dindo ≥ IIIb were significantly increased in patients with PPAP, and CR-PF, intra-abdominal infection, abdominal fluid collection, puncture, and drainage treatment, and mortality were also significantly increased. The total lengths of hospital stay and postoperative hospital stay were longer in the PPAP group. The hospitalization cost in the PPAP group was also significantly increased by $1,721 ($15,671 and $13,950, respectively).

To further evaluate the effects of PPAP on serious postoperative complications, univariate and multivariate analyses were conducted on patients with Clavien–Dindo ≥ IIIb (**Table 2**). This indicated that PPH (OR 12.807, 95% CI 2.401–131.105), intra-abdominal infection (OR 11.101, 95% CI 1.158–1617.774), AKI (OR 97.612, 95% CI 2.942–34098.204), and postoperative hypoalbuminemia (OR 4.166, 95% CI 1.063–19.866) were independent predictors of Clavien–Dindo ≥ IIIb. It' is worth noting that in univariate analyses, there was statistical difference in PPAP, suggesting that PPAP did not increase the incidence of Clavien–Dindo ≥ IIIb directly.

TABLE 1 | Postoperative outcomes stratified by the occurrence of PPAP.

	PPAP		Z/χ^2	*p*-value
	No (*n* = 136)	Yes (*n* = 150)		
Clavien–Dindo, *n* (%)			5.637	0.018
<IIIb	133 (97.8)	137 (91.3)		
≥IIIb	3 (2.2)	13 (8.7)		
CR-PF, *n* (%)			18.942	<0.001
B	15 (11.0)	41 (27.3)		
C	2 (1.5)	9 (6.0)		
PPH, *n* (%)			6.016	0.111
A	9 (6.6)	11 (7.3)		
B	2 (1.5)	8 (5.3)		
C	5 (3.7)	12 (8.0)		
DGE, *n* (%)			4.203	0.240
A	34 (25.0)	28 (18.7)		
B	20 (14.7)	32 (21.3)		
C	6 (4.4)	11 (7.3)		
BL, *n* (%)	3 (2.2)	1 (0.7)	0.363	0.547
Intra-abdominal infection, *n* (%)	52 (38.2)	78 (52.0)	5.451	0.020
AKI, *n* (%)	2 (1.5)	2 (1.3)	0.010	0.921
Bowel obstruction, *n* (%)	4 (2.9)	4 (2.7)	0.020	0.888
Abdominal fluid collection, *n* (%)	28 (20.6)	71 (47.3)	22.543	<0.001
percutaneous drainage, *n* (%)	9 (6.6)	28 (18.7)	9.194	0.002
Secondary operation, *n* (%)	4 (2.9)	12 (8.0)	3.456	0.063
Mortality, *n* (%)	0 (0)	6 (2.1)	5.557	0.018
ICU stay (day)	1.0 (0–2.0)	1.0 (0–2.0)	−0.332	0.740
Total hospital stay (day)	23.0 (18.0–28.0)	24.0 (20.0–31.0)	−2.000	0.045
Postoperative hospital stay (day)	15.5 (12.0–19.0)	17.0 (14.0–21.3)	−2.520	0.012
Cost ($)	13,950 (11,601–17,041)	15,671 (12,925–19,124)	−2.778	0.005

PPAP, postpancreatectomy acute pancreatitis; CR-PF, clinical relevant pancreatic fistula; PPH, postpancreatectomy hemorrhage; DGE, delayed gastric empty; BL, bile leakage; AKI, acute kidney injury; ICU, intensive care unit.

Risk Factors for PPAP After PD

Stratified by the PPAP occurrence, the perioperative characteristics as well as univariate and multivariate analyses are shown in **Table 3**. Female, BMI ≥ 25, preoperative jaundice state, pancreatic texture, diameter of pancreatic duct, the techniques of pancreatic anastomosis, and CRP ≥ 180 mg/L were enrolled into the multivariate analysis model. Due to multicollinearity of the diameter of pancreatic duct and pancreatic texture, fistula risk scores were excluded from multivariate analysis. The soft texture of pancreatic stump and CRP ≥ 180 mg/L were defined as independent predictors of

TABLE 2 | Univariate and multivariate analyses of Clavien–Dindo ≥ IIIb postoperative complications.

	Univariate			Multivariate		
	No ($n = 270$)	Yes ($n = 16$)	p-value	OR	95% CI	p-value
PPAP, *n* (%)	137(50.7)	13(81.3)	0.018	2.464	0.358–13.477	0.268
CR-PF, *n* (%)	56 (20.7)	11 (68.8)	<0.001	1.642	0.107–3.043	0.545
PPH, *n* (%)	34 (12.6)	13 (81.3)	<0.001	12.807	2.401–131.105	0.002
DGE, *n* (%)	115 (42.6)	16 (100)	<0.001	6.373	0.592–759.752	0.137
BL, *n* (%)	3 (1.1)	1 (6.3)	0.207			
Intra-abdominal infection, *n* (%)	114 (42.2)	16 (100)	<0.001	11.101	1.158–1617.774	0.034
Abdominal fluid collection, *n* (%)	86 (31.9)	13 (81.3)	<0.001	1.925	0.358–13.477	0.445
AKI, *n* (%)	1 (0.4)	3 (18.8)	0.001	97.612	2.942–34,098.204	0.005
Bowel obstruction, *n* (%)	8 (3.0)	0 (0)	1			
Wound infection, *n* (%)	2 (0.7)	1 (6.3)	0.159	24.047	0.085–10,249.661	0.608
Hypoalbuminemia, *n* (%)	96 (35.6)	13 (81.3)	<0.001	4.166	1.063–19.866	0.041
Hypocalcemia, *n* (%)	169 (62.6)	11 (68.8)	0.620			

PPAP, postpancreatectomy acute pancreatitis; CR-PF, clinically relevant pancreatic fistula; PPH, post-pancreatectomy hemorrhage; DGE, delayed gastric empty; BL, bile leakage; AKI, acute kidney injury.

PPAP through multivariate analysis (OR 2.953, 95% CI 1.764–4.943 and OR 3.591, 95% CI 2.047–6.297, respectively). The area under the ROC curve was 0.613 (**Figure 3**).

In this study, 10 patients occurred gade C PPAP in the patients' cohort, and the incidence of grade C PPAP was 3.5%. Grade C PPAP was a rare but life-threatening complication after PD. Stratified by the grade of PPAP, the perioperative characteristics as well as univariate analysis are shown in **Table 4**. Compared to the non-PPAP group, male, BMI ≥ 25, preoperative jaundice state, pancreatic duct diameter <5 mm, soft pancreatic texture, the methods of pancreatic anastomosis, and CRP ≥ 180 mg/L were enrolled into the multivariate analysis model for predicting grade B PPAP. For the reasons mentioned above, fistula risk scores were excluded from multivariate analysis. As shown in **Table 5**, soft pancreatic texture (OR 2.732, 95% CI 1.590–4.695) and CRP ≥ 180 mg/L (OR 3.444, 95% CI 1.954–6.069) were the independent predictors of grade B PPAP. For predicting the model of grade C PPAP, tobacco and alcohol use, hypertension, pancreatic duct diameter <5 mm, soft pancreatic texture, liquid intake/output volume ≤ 2000 ml, operation duration >360 min, the methods of pancreatic anastomosis, and CRP ≥ 180 mg/L were enrolled compared to the non-PPAP group. As shown in **Table 6**, soft pancreatic texture (OR 19.298, 95% CI 1.840–2812.980), operation duration >360 min (OR 13.832, 95% CI 1.719–910.506), and the pancreatic anastomosis by using conventional duct-to-mucosa methods (OR 10.402, 95%CI 1.409-694.367) were the independent predictors of grade C PPAP.

Influence of PPAP and PF on Postoperative Complications

To explore the influence of PPAP and PF on postoperative complications, the patients was divided into none of PPAP and PF occurred group, only PPAP occurred group, only PF group, and both PPAP and PF occurred group. The postoperative complications among different groups are given in **Table 4**. It shows that the occurrence of PPAP was independent of PF by observing 100 patients with PPAP but was not complicated with PF. Meanwhile, 50 patients suffered from both PPAP and PF.

Two questions of concern to us were statistically analyzed. First, what were the clinical consequences for the patients with PPAP compared to the patients with neither PPAP nor PF? Shown in **Table 7**, PPAP occurrence just significantly increased the incidence of abdominal fluid collection ($p < 0.001$); however, other severe complications such as PPH were not significantly increased. What is more, the only PPAP occurred group had longer postoperative hospital stay and spent more money on hospitalization but did not show significant difference at the level of p value <0.05. Second, what were clinical impacts of PPAP complicated with PF compared to PPAP alone? PPAP complicated with PF significantly increased the mortality and incidence of Clavien–Dindo ≥ IIIb complications, PPH, DGE, intraabdominal infection, abdominal fluid collection, percutaneous drainage, and unplanned secondary operation compared to the only PPAP occurred group. In addition, PPAP complicated with PF significantly increased the length of ICU and hospital stay and hospital expenses.

DISCUSSION

Incidence of PPAP

Postoperative pancreatitis after PD was brought into our attention after a patient died inevitably from severe pancreatitis in remnant pancreas in January 2016; then, we started to do targeted inspections (serum enzymology and CT

TABLE 3 | Univariate and multivariate analyses of PPAP.

	Univariate analysis			Multivariate analysis		
	No (*n* = 136)	**Yes (*n* = 150)**	***p*-value**	**OR**	**95% CI**	***p*-value**
Sex ratio (M:F)	95:41	81:69	0.006*	1.560	0.871–2.794	0.135
Age (year)	62 (55–69)	62 (56–69)	0.786			
BMI ≥ 25, *n* (%)	81 (59.6)	74 (49.3)	0.083	1.389	0.788–2.448	0.256
Tobacco use, *n* (%)	44 (32.4)	40 (26.7)	0.292			
Alcohol use, *n* (%)	14 (10.3)	13 (8.7)	0.638			
AP history, *n* (%)	10 (7.4)	13 (8.7)	0.683			
DM, *n* (%)	20 (14.7)	18 (12.0)	0.501			
Hypertension, *n* (%)	35 (25.7)	40 (26.7)	0.858			
Cholelithiasis, *n* (%)	32 (23.5)	39 (26.0)	0.629			
Preoperative jaundice state, *n* (%)	88 (64.7)	81 (54.0)	0.066	1.292	0.750–2.223	0.356
Previous abdominal surgery, *n* (%)	30 (22.1)	32 (21.3)	0.882			
ASA, *n* (%)			0.260			
1	1 (0.7)	4 (2.7)				
2	102 (75.0)	102 (68.0)				
≥3	33 (24.3)	44 (29.3)				
Vascular resection, *n* (%)	15 (11.0)	18 (12.0)	0.798			
Extended organ resection, *n* (%)	2 (1.5)	4 (2.7)	0.770			
Pancreatic duct diameter <5 mm, *n* (%)	74 (54.4)	105 (70.0)	0.007	1.534	0.883–2.663	0.129
Pancreatic texture, *n* (%)			<0.001	2.966	1.733–5.076	<0.001
Soft	46(33.8)	96(64.0)				
Hard	90(66.2)	54(36.0)				
Pancreatic stent, *n* (%)			0.395			
Unused	14(10.3)	9(6.0)				
Internal	89(65.4)	105(70.0)				
External	33(24.3)	36(24.0)				
Bleeding ≥ 400 ml, *n* (%)	80 (58.8)	77 (51.3)	0.204			
liquid intake/output volume ≤ 2000 ml, *n* (%)	34 (25.0)	39 (26.0)	0.846			
Operation duration (min)	360 (300–420)	360 (296–434)	0.291			
Fistula risk scores, *n* (%)			0.017	/		
Negligible	17 (12.5)	13 (8.7)		/		
Low	50 (36.8)	34 (22.7)		/		
Moderate	63 (46.3)	97 (64.7)		/		
High	6 (4.4)	6 (4.0)		/		
Pathology type, *n* (%)			0.386			
PDAC and CP	50 (36.8)	45 (30.0)				
Other malignant	75 (55.1)	88 (58.7)				
Benign and low malignant	11 (8.1)	17 (11.3)				
Pancreatic anastomosis, *n* (%)			<0.001			
Modified Blumgart	85 (62.5)	63 (42.0)		0.767	0.304–1.934	0.574
Conventional duct to mucosa	36 (26.5)	75 (50.0)		1.854	0.712–4.829	0.206
Invagination	15 (11.0)	12 (8.0)		1		
Pancreatic enzymes inhibitors, *n* (%)			0.086			
Unused	3 (2.2)	0				
Octreotide	63 (46.3)	60 (40.0)				
Somatostatin	70 (51.5)	90 (60.0)				

(*continued*)

TABLE 3 | Continued

	Univariate analysis			Multivariate analysis		
	No ($n = 136$)	Yes ($n = 150$)	*p*-value	OR	95% CI	*p*-value
Ulinastatin use	39 (28.7)	50 (33.3)	0.396			
Hypoalbuminemia, *n* (%)	54 (39.7)	55 (36.7)	0.597			
CRP ≥ 180 mg/l, *n* (%)	30 (22.1)	77 (51.3)	<0.001	3.591	2.047–6.297	<0.001
Hypocalcemia, *n* (%)	88 (64.7)	92 (61.3)	0.555			
ΔTB, *n* (%)			0.623			
Decrease	61 (44.9)	59 (39.3%)				
Unchanged	21 (15.4%)	27 (18.0%)				
Elevation	54 (39.7%)	64 (42.7%)				
POD 1 drainage volume (ml)	67.5 (31.3–157.5)	80.0 (32.5–215.0)	0.535			
POD 2 drainage volume (ml)	72.5 (30.0–160.0)	90.0 (25.0–200.0)	0.748			
POD 3 drainage volume (ml)	81.0 (20.8–178.8)	80.0 (20.0–182.5)	0.865			

PPAP, postpancreatectomy acute pancreatitis; AP, acute pancreatitis; DM, diabetes mellitus; ASA, American Society of Anesthesiologists; PDAC, pancreatic duct adenocarcinoma; CP, chronic pancreatitis; ΔTB, postoperative minus preoperative total bilirubin value; POD, postoperative days.

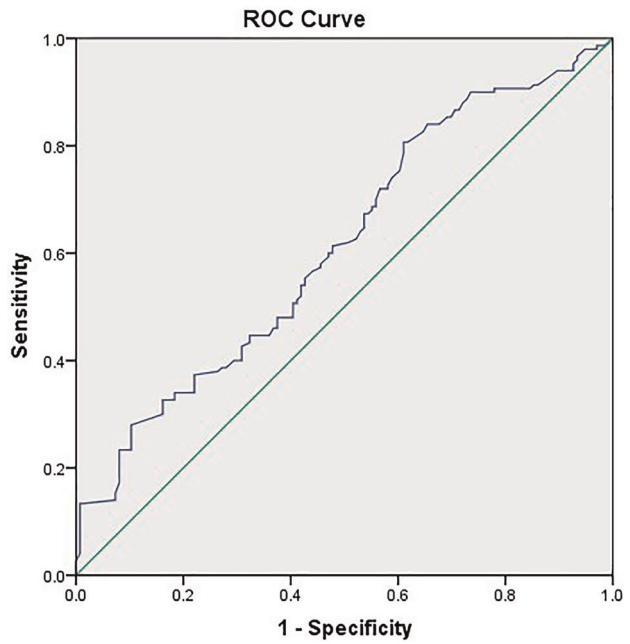

FIGURE 3 | Receiver operating characteristic (ROC) curve for threshold analysis of predicting PPAP (AUC 0.613).

examination) on suspected patients to provide an actual aid for patients' management. Therefore, the patients' cohort in this retrospective study had relatively complete data of serum enzymology and abdominal CT images. We retrieved the PubMed database; acute pancreatitis after partial pancreatectomy was first reported in 1952 (23). Recent literature started to focus on PPAP, and the occurrence of PPAP was an independent predictor of PF (5). However, there was considerable heterogeneity in previous studies due to the lack of uniform diagnostic criteria and grading system. Recently, ISGPS published the definition of PPAP (11), which was a milestone in the research of PPAP.

The incidence of PPAP varied greatly between current and past studies. According to Kriger et al. (24), the incidence of PPAP was 58.9% (178/302) by the Atlanta classification and definitions (12). Based on Connor's definition, Nahm et al. (7) found the incidence of PPAP was 62% (38/61). Most recently, Bassi et al. (5) reviewed 292 PD patients, and the incidence was 55.8% (163/292) in 2018. In the same year, the German team (6) reported that the incidence was 53% (100/190). Here, we practiced this definition published by ISGPS, and the incidence of PPAP was 52.4% in this study, which was at the same level as in current studies. However, past literature works reported the incidence of PPAP at a very low level of about 2%–3% (25, 26). Possibly due to a lack of standardized definitions in past, PPAP was diagnosed only in the condition of typical or severe clinical symptoms or life-threatening complications caused by pancreatitis. In other words, postpancreatectomy pancreatitis mentioned in the past literature probably meant the grade C PPAP (11). In this study, the incidence of grade C PPAP was 3.5%, which was comparable to the past literature (25, 26). This result provided a possible explanation for the polarization of PPAP incidence in the literature. Recent study (27) showed that necrotizing pancreatitis of the remnant pancreas confirmed by histological section was found in 33 out of 79 (41%) patients who underwent completion pancreatectomy after initial PD due to unfavorable complications. The postoperative pancreatitis not only occurred in the PD or other partial pancreatectomy but also was reported in scoliosis surgery (28), aortic dissection (29), renal transplantation (30), and gynecologic and obstetric surgery (31), and the incidence ranged from 0.29% to 5.9%.

TABLE 4 | Univariate analysis of grade C PPAP.

	No. (*n* = 136)	PPAP		*p*-value[a]	*p*-value[b]
		Grade B (*n* = 140)	Grade C (*n* = 10)		
Sex ratio (M: F)	95:41	74:66	7:3	0.004	0.992
Age (year)	62 (55–69)	62 (56–69)	64 (55–70)	1.000	0.612
BMI ≥ 25, *n* (%)	81 (59.6)	67 (47.9)	7 (70.0)	0.051	0.515
Tobacco use, *n* (%)	44 (32.4)	34 (24.3)	6 (60.0)	0.137	0.075
Alcohol use, *n* (%)	14 (10.3)	10 (7.1)	3 (30.0)	0.353	0.061
AP History, *n* (%)	10 (7.4)	13 (9.3)	0 (0)	0.561	0.374
DM, *n* (%)	20 (14.7)	15 (10.7)	3 (30.0)	0.319	0.200
Hypertension, *n* (%)	35 (25.7)	34 (24.3)	6 (60.0)	0.781	0.020
Cholelithiasis, *n* (%)	32 (23.5)	38 (27.1)	1 (10.0)	0.490	0.324
Preoperative jaundice state, *n* (%)	88 (64.7)	73 (52.1)	8 (80.0)	0.034	0.325
Previous abdominal surgery, *n* (%)	30 (22.1)	30 (21.4)	2 (20.0)	0.899	0.879
ASA, *n* (%)				0.306	0.198
1	1 (0.7)	4 (2.9)	0 (0)		
2	102 (75.0)	97 (69.3)	5 (50.0)		
≥3	33 (24.3)	39 (27.9)	5 (50.0)		
Vascular resection, *n* (%)	5 (11.0)	17 (12.1)	1 (10.0)	0.773	0.920
Pancreatic duct diameter <5 mm, *n* (%)	74 (54.4)	96 (68.6)	9 (90.0)	0.016	0.028
Pancreatic texture, *n* (%)				<0.001	<0.001
Soft	46 (33.8)	86 (61.4)	10 (100.0)		
Hard	90 (66.2)	54 (38.6)	0 (0)		
Pancreatic stent, *n* (%)				0.508	0.262
Unused	14 (10.3)	9 (6.4)	0 (0)		
Internal	89 (65.4)	96 (68.6)	9 (90.0)		
External	33 (24.3)	35 (25.0)	1 (10.0)		
Bleeding ≥ 400 ml, *n* (%)	80 (58.8)	73 (52.1)	4 (40.0)	0.264	0.245
liquid intake/output volume ≤ 2000 ml, *n* (%)	34 (25.0)	34 (24.3)	5 (50.0)	0.890	0.085
Operation duration > 360 min, *n* (%)	64 (47.1)	65 (46.4)	9 (90.0)	0.916	0.009
Fistula risk scores, *n* (%)				0.044	0.066
Negligible	17 (12.5)	13 (9.3)	0 (0)		
Low	50 (36.8)	33 (23.6)	1 (10.0)		
Moderate	63 (46.3)	88 (62.9)	9 (90.0)		
High	6 (4.4)	6 (4.3)	0 (0)		
Pathology type, *n* (%)				0.395	0.153
PDAC and CP	50 (36.8)	44 (31.4)	1 (30.0)		
Other malignant	75 (55.1)	81 (57.9%)	2(58.7)		
Benign and low malignant	11 (8.1)	15 (10.7)	7 (11.3)		
Pancreatic anastomosis, *n* (%)				0.001	0.013
Modified Blumgart	85 (62.5)	60 (42.9)	3 (30.0)		
Conventional duct to mucosa	36 (26.5)	68 (48.6)	7 (70.0)		
Invagination	15 (11.0)	12 (8.6)	0 (0)		
CRP ≥ 180 mg/L, *n* (%)	30 (22.1)	70 (50.0)	7 (70.0)	<0.001	0.001

[a]*Grade B PPAP group compared to the non-PPAP group.*
[b]*Grade C PPAP group compared to the non-PPAP group; PPAP, postpancreatectomy acute pancreatitis; AP, acute pancreatitis; DM, diabetes mellitus; ASA, American Society of Anesthesiologists; PDAC, pancreatic duct adenocarcinoma; CP, chronic pancreatitis.*

Diagnostic Parameters of PPAP

The diagnostic criteria of PPAP consisted of three parameters: biochemical, radiological, and clinical evidence. The elevated serum amylase greater than the upper limit showed the same diagnostic efficacy as the elevation of three times (32). Early and sustained elevation of serum amylase was thought to be more associated with postoperative complications than its peak value detected (33). The available literature (4) agreed that PPAP occurred in the early phase of postoperative period (POD 0–3). Thus, it is distinguished from the time of PF occurrence, which was defined at the later phase (POD ≥ 3) (17). Abdominal pain is an essential criterion in usual acute pancreatitis. However, abdominal pain is not a reliable diagnostic criterion after partial pancreatectomy because it could be concealed by postoperative analgesia to varying degrees (11). Early postoperative CT scans were helpful to evaluate the recovery in the surgical field. The remnant

TABLE 5 | Multivariate analysis of grade B PPAP.

	OR	Multivariate	
		95% CI	*p*-value
Sex ratio (M: F)	1.577	0.879–2.827	0.126
BMI ≥ 25	0.706	0.400–1.247	0.231
Preoperative jaundice state	0.739	0.428–1.276	0.278
Pancreatic duct diameter <5 mm	1.461	0.840–2.540	0.179
Pancreatic texture (soft)	2.732	1.590–4.695	<0.001
Pancreatic anastomosis			
Modified Blumgart	0.759	0.302–1.908	0.558
Conventional duct to mucosa	1.739	0.669–4.505	0.256
Invagination	1		
CRP ≥ 180 mg/L	3.444	1.954–6.069	<0.001

TABLE 6 | Multivariate analysis of grade C PPAP.

		Multivariate	
	OR	95% CI	*p*-value
Tobacco use	1.394	0.008–11.554	0.826
Alcohol use	5.534	0.248–5630.762	0.288
Hypertension	3.511	0.430–34.883	0.228
Pancreatic duct diameter <5 mm	3.987	0.376–545.662	0.269
Pancreatic texture (soft)	19.298	1.840–2812.980	0.010
liquid intake/output volume ≤ 2000 ml	1.650	0.222–14.454	0.613
Operation duration > 360 min	13.832	1.719–910.506	0.011
Pancreatic anastomosis			
Modified Blumgart	0.317	0.001–8.372	0.533
Conventional duct to mucosa	10.402	1.409–694.367	0.020
Invagination	1		
CRP ≥ 180 mg/L	3.004	0.384–26.977	0.271

pancreas (pancreatic body and tail) was not conventionally dissected during PD procedure; however, the signs of pancreatic exudation or parenchymal changes in postoperative CT scans suggest the formation of PPAP (34). Palumbo et al. (35) suggested that the routinely postoperative CT scan after laparoscopic sleeve gastrectomy was helpful to early stratification of leakage risk. Contrast-enhanced CT in our retrospective study was less adopted except when necessary, mainly because it usually has a long waiting time for examination and might put extra burden on the kidneys, which was not suitable for patients in early postoperative phase.

Clinical Significance of PPAP

PPAP was significantly associated with unfavorable outcomes in our study. PPAP and PF are reciprocal causation, and they can also occur independently. In this study, PF complicated with PPAP was found in 50 (74.6%) out of 67 PF patients. On the one hand, PPAP could cause cellular injury by releasing active zymogens and stimulate inflammatory response in the pancreatic parenchyma (36). In the setting of pancreatojejunostomy, zymogens can be activated by digestive juice in reconstructed digestive tract, which causes autodigestive injury in anastomotic tissue. PPAP could probably prolong the healing time of anastomosis and provide a pre-condition for the occurrence of pancreatic leakage, which then leads to PF (11). On the other hand, activated pancreatic juice leaking from dehiscence of the anastomosis pervades the remnant pancreas, which causes inflammatory damage (10). Besides, we found that 66.7% (100/150) PPAP, which was not complicated with PF, did not lead to serious complications; however, PF complicated with PPAP could cause serious complications and increase the mortality rate (10.0%). Rudis et al. found that grade C PF complicated with PPAP was observed in 4 out of 160 patients, and none of these patients survived (37). We also noticed that a large proportion of PPAP with unfavorable outcomes was complicated with PF, and PF appeared to be the major factor on outcome. Only the occurrence of PPAP may not lead to serious clinical impacts, unless grade C PPAP, which could be the cause of persistent organ failure and other severe complications.

Risk Factors for PPAP

In this study, we found that soft pancreatic texture and CRP ≥ 180 mg/L were the independent predictors of grade B PPAP. In addition, soft pancreatic texture, operation duration >360 min, and pancreatic anastomosis by using conventional duct-to-mucosa methods were the independent risk factors for grade C PPAP. Due to the small sample size in our study, some variables occurred complete separation and quasi-complete separation. To improve the stability of the prediction model, we used Firth logistic regression to perform multivariate analysis. A retrospective study from the University of Heidelberg (6) reported a comparable incidence of PPAP and the association with CRP to our study. Notably, the pancreatic texture was observed in all patients with grade C PPAP. However, the soft texture of pancreas is a subjective index. Nahm et al. (7) reported that the acinar cell density at the pancreatic resection margin can better describe the residual pancreas than "texture," and the density of acinar was significantly associated with PPAP. Univariate analysis showed that PPAP was more likely to take place in females, and female is also one of the independent risk factors for PEP (38). Women have a higher percentage of body fat than men, which makes the pancreas softer; hpwever, gender did not show statistical difference in multivariate analysis in this study. Bassi et al. (5) found that independent risk factors for PPAP included preoperative exocrine insufficiency, neoadjuvant therapy, additional resection of the pancreatic stump margin, soft pancreatic texture, and main pancreatic duct diameter ≤3 mm. From our retrospective data, details of extended pancreatic stump resection were not routinely recorded, and in 92 patients with pancreatic ductal adenocarcinoma, only 5 (5.4%) patients with borderline resectable pancreatic cancer received neoadjuvant chemotherapy and (or) radiotherapy, so these variables were not analyzed. Intraoperative pancreatic ischemia was thought to be a

TABLE 7 | Postoperative complications grouped by PPAP and PF occurrence.

	PPAP and PF occurrence				*p*-value	
	None (*n* = 119)	Only PPAP (*n* = 100)	Only PF (*n* = 17)	Both (*n* = 50)	P^1	P^2
Clavien-Dindo ≥ IIIb, *n* (%)	2 (1.7)	3 (3.0)	1 (5.9)	10 (20.0)	0.844	0.001
PPH, *n* (%)	11 (9.2)	13 (13.0)	5 (29.4)	18 (36.0)	0.452	0.001
A	7 (63.6)	7 (53.8)	2 (40.0)	4 (22.2)		
B	1 (9.1)	4 (30.8)	1 (20.0)	4 (22.2)		
C	3 (27.3)	2 (15.4)	2 (40.0)	10 (55.6)		
DGE, *n* (%)	47 (39.5)	36 (36.0)	13 (76.5)	35 (70.0)	0.359	<0.001
A	31 (66.0)	17 (47.2)	3 (23.1)	11 (31.4)		
B	14 (29.8)	17 (47.2)	6 (46.2)	15 (42.9)		
C	2 (4.2)	2 (5.6)	4 (30.7)	9 (25.7)		
BL, *n* (%)	1 (0.8)	0	2 (11.8)	1 (2.0)	1	0.333
Intra-abdominal infection, *n* (%)	36 (30.3)	33 (33.0)	16 (94.1)	45 (90.0)	0.663	<0.001
AKI, *n* (%)	1 (0.8)	1 (1.0)	1 (5.9)	1 (2.0)	1	1
Bowel obstruction, *n* (%)	4 (3.4)	3 (3.0)	0 (0)	1 (2.0)	1	1
Wound infection, *n* (%)	1 (0.8)	0 (0)	0 (0)	2 (4.0)	1	0.110
Abdominal fluid collection, *n* (%)	19 (16.0)	38 (38.0)	9 (52.9)	33 (66.0)	<0.001	0.001
Puncture and drainage treatment, *n* (%)	4 (3.4)	7 (7.0)	5 (29.4)	21 (42.0)	0.219	<0.001
Secondary operation, *n* (%)	3 (2.5)	3 (3.0)	1 (5.9)	9 (18.0)	1	0.004
Mortality, *n* (%)	0 (0)	1 (1.0)	0 (0)	5 (10.0)	0.457	0.027
ICU stay (day)	1.0 (0–2.0)	1.0 (0–2.0)	2.0 (1.0–5.0)	2.0 (0–3.0)	0.874	0.007
Total hospital stay (day)	22.0(18.0–27.0)	22.5(19.0–28.0)	42.0(23.5–54.0)	29.0(23.8–37.0)	0.401	<0.001
Postoperative hospital stays (day)	15.0(12.0–18.0)	16.0(14.0–18.8)	27.0(16.5–39.0)	20.5(15.8–30.5)	0.054	<0.001
Cost ($)	13,685(11,250–16,491)	14,678(12,145–170,723)	23,299(15,373–31,391)	17,758(15,497–23,908)	0.055	<0.001

p^1, only PPAP group compared to the none of PPAP and PF occurred group; p^2: both PPAP and PF occurred group compared with the only PPAP group; PPAP, postpancreatectomy acute pancreatitis; PF, clinical relevant pancreatic fistula; PPH, postpancreatectomy hemorrhage; DGE, delayed gastric empty; BL, bile leakage; AKI, acute kidney injury; ICU, intensive care unit.

mechanism for pancreatitis (39, 40); nevertheless, this study cannot produce effective comparisons between the two groups. For the average liquid intake/output volume on the surgery day, our patients' cohort was far beyond the "near-zero fluid" (5) (PPAP group: 2729 ml, non-PPAP group: 2721 ml).

Managements of PPAP

Currently, the methods to prevent PPAP were very limited due to the lack of RCTs and prospective studies. The usage of pancreatic enzyme inhibitors, including octreotide and somatostatin, was not a protective factor for PPAP occurrence in this study. This was in accordance with the results of PF study (41–43). Somatostatin drugs can reduce splanchnic blood flow (44), which may increase the occurrence of pancreatitis and PF. One RCT study (45) demonstrated that prophylactic administration of ulinastatin can reduce the incidence of PPAP and also reduce the levels of amylase in serum and drain. Hydrocortisone (46) and rectal indomethacin (47) had proved that they can reduce the incidence of postoperative complications; however, these factors were not enrolled in this study due to very small sample size ($n = 2$).

The deficiency of this study was its retrospective design. Moreover, the patients were not stratified by preoperative features and surgical techniques to avoid small sample sizes, which may reduce the statistical efficiency and make clinical significance unstable. The data of preoperative amylase were lacking in this study, and the delta could better describe the inflammatory changes in the remnant pancreas than the specified threshold (48). The study is focused on the early postoperative period; however, and the impacts of PPAP on the long-term, such as recurrent pancreatitis, chronic pancreatitis, diabetes, fatty liver, and survival, were not calculated.

In conclusion, based on the structured definition and grading system of PPAP published by ISGPS, we found the incidence of PPAP after PD was at a high level (52.4%), which was in accordance with current research. Stratified by the grade of PPAP, soft pancreatic texture and CRP ≥ 180 mg/L were the independent predictors of grade B PPAP, and soft pancreatic texture, operation duration >360 min, and the pancreatic anastomosis by using conventional duct-to-mucosa methods were the independent predictors of grade C PPAP. PPAP had certain clinical practical significance on the clinical outcomes,

especially when it was complicated with PF. Higher-volume multicenter and prospective studies are needed to promote a better understanding of PPAP.

DATA AVAILABILITY STATEMENTS

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Xi'an Jiao tong University. The patients/participants provided their written informed consent to participate in this study.

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SW and HW collected the data and wrote the original draft. SW and FX analyzed data. GX performed the radiological evaluation. YZ, SD and LH analyzed and interpreted the data. ZW and ZW revised the manuscript. ZW conceived and designed the study. All authors contributed to the article and approved the submitted version script.

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SUPPLEMENTARY MATERIAL

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Development and validation of a competing risk model for second primary pancreatic ductal adenocarcinoma: A population-based study

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Background: With advances in early diagnosis and treatment, the number of cancer survivors continues to grow, and more and more cancer survivors face the threat of second primary cancer (SPM). Second primary pancreatic ductal adenocarcinoma (spPDAC) is an important subclass of SPM, but its prognostic characteristics are poorly understood.

Methods: A total of 5,439 spPDAC samples and 67,262 primary pancreatic ductal adenocarcinoma (pPDAC) samples were extracted from the SEER database for this study. Survival differences between spPDAC and pPDAC samples were compared using Kaplan–Meier curves and log-rank tests. The Fine and Gray proportional subdistributed hazard method was used to analyze potential associations between clinical variables and pancreatic ductal adenocarcinoma-specific death (PDACSD) and death from other causes. After that, the clinical variables significantly related to PDACSD were screened out to construct a competing risk nomogram, which was used to evaluate the probability of the occurrence of PDACSD. The C-index was used to evaluate the discriminative ability of the model. The area under the curve (AUC) was used to verify the discrimination of the model. The calibration curve was used to verify the calibration of the model. Decision curve analysis (DCA) was used to validate the clinical utility of the model.

Results: Compared with patients with spPDAC, the pPDAC sample had a better prognosis ($p = 0.0017$). Across all spPDAC samples, the three most common sites of first-present cancer were the prostate, breast, and digestive system. Age ($p < 0.001$), race ($p = 0.006$), interval ($p = 0.016$), location ($p < 0.001$), T stage ($p = 0.003$), M stage ($p < 0.001$), chemotherapy ($p < 0.001$), and radiotherapy ($p = 0.006$) were the clinical variables associated with PDACSD screened by multivariate competing risks analysis. The concordance index values for the training and validation sets were 0.665 (95% CI, 0.655, 0.675)

Abbreviations

SPM, second primary malignancies; spPDAC, second primary pancreatic ductal adenocarcinoma; pPDAC, primary pancreatic ductal adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results; KM, Kaplan–Meier; PDACSD, pancreatic ductal adenocarcinoma-specific death; DFOC, death from other causes; CIF, cumulative incidence function; C-index, concordance index; AUC, the area under the curve; DCA, decision curve analysis; FPC, first-present cancer; IQR, interquartile range; SD, standard deviation.

and 0.666 (95% CI, 0.650, 0.682), respectively. AUC, calibration curve, and DCA indicated that the model we constructed had good discrimination, calibration, and clinical utility.

Conclusions: In conclusion, we first analyzed the impact of previous cancer history on prognosis. We then constructed a competing risk model that can predict the probability of developing PDACSD in spPDAC. This model has good discriminative ability, calibration, and clinical practicability and has certain guiding value for clinical decision-making.

KEYWORDS

second primary malignancy, SEER database, competing regression analysis, nomogram risk, pancreatic ductal adenocarcinoma

Introduction

Second primary malignancy (SPM) refers to the reappearance of a new primary malignant tumor based on the original malignant tumor (1). The number of cancer survivors is also growing due to early diagnosis, advances in treatment technology, and an aging population (2). Some statistical agencies predict that in 2026, there will be 20 million cancer survivors (3). Cancer survivors represent approximately 3.5% of the general population in the United States, and approximately one in ten newly diagnosed cancers occurs in cancer survivors (4, 5). Statistics show that with an increase in the number of cancer survivors, the number of patients with SPM also has a steady upward trend (6, 7). SPM has emerged as a significant risk factor for cancer survivors. First primary cancers (FPCs) and their treatments may influence the biological progression, treatment, and prognosis of SPM (8–11). This has led many studies to exclude this particular group. However, the increasing number of SPM patients urgently needs more research to provide guidance for clinical decision-making.

Second primary pancreatic ductal adenocarcinoma (spPDAC) is an important component of SPM. As one of the most common cancers worldwide, pancreatic ductal adenocarcinoma (PDAC) is the seventh leading cause of cancer-related death (12, 13). As more and more cancer survivors are at risk from SPM, the development of PDAC to SPM is also more frequent (14, 15). A pooled analysis study of international multicenter cancer registries reported that spPDAC accounted for 6.9% of all PDAC diagnoses (15). A Korean study showed that the type of FPC can affect the probability and prognosis of spPDAC (16). In a cohort study based on 273,144 samples, an increased incidence of pancreatic cancer was found in a population of patients with previous colon cancer (17). Due to the characteristics of multiple primary cancers, a large number of studies have excluded this special group. Furthermore, because the occurrence of spPDAC cases is relatively rare and difficult to collect, there is currently a lack of research on the prognostic characteristics of spPDAC. There are few studies on spPDAC, and the risk factors associated with spPDAC remain unclear.

The aim of this study was to analyze the impact of previous cancer on the prognosis of spPDAC patients and to identify clinical and demographic factors associated with spPDAC survival. Based on the Fine and Gray proportional subdistributed hazard method, we attempted to create competing risk nomograms to predict half-year, 1-year, and 2-year pancreatic ductal adenocarcinoma-specific mortality for spPDAC.

Materials and methods

Data sources

The data used in this study were extracted from the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/). Using SEER*Stat (version 8.4.0) data extraction software, eligible samples from the 18 population-based registriy (2000–2018) datasets were downloaded (18). Based on submissions in November 2020 and released in April 2021, the dataset covers 18 regions, including San Francisco-Oakland SMSA, Connecticut, and Detroit (Metropolitan), and accounts for 27.8% of the total US population. For Group A, 16,392 samples with a history of cancer were extracted. The retrieval conditions are as follows: (1) the first tumor was malignant; (2) the second primary cancer was in the pancreas; and (3) the histological diagnosis was positive. Extract clinical variables of interest include gender, ethnicity, age and year at diagnosis, site of cancer occurrence, pathological type, marital status, location of spPDAC, TNM stage of spPDAC, treatment of spPDAC, FPC site, and FPC histology type. For Group B, 67,945 pPDAC samples were extracted. The search criteria are as follows: (1) age not less than 20 years old; (2) the time of diagnosis was between 2004 and 2015; (3) the topographic code located in the pancreas was selected (ICD-O-3: C25.0–C25.3, C25 .7–C25.9) with ICD-O-3 histology/behavior code 8140/3

(adenocarcinoma) or 8500/3 (invasive ductal adenocarcinoma); and (4) only one primary malignancy occurred. This study was exempt from institutional review board approval due to the public nature and deidentification of all data.

Data processing

Of the 16,392 original samples in group A, 5,439 samples were finally screened for follow-up studies. The exclusion criteria are as follows: (1) delete samples with three or more primary tumors (n = 2,347); (2) delete samples with pancreatic cancer as the third and fourth primary cancers (n = 117); (3) samples (n = 4,760) whose spPDAC diagnosis time was not within the time range from 2004 to 2015 were deleted; (4) delete missing data (n = 62); (5) delete missing clinical variables (n = 866); (6) delete samples where the FPC was pancreatic cancer (n = 53) and samples (n = 586) where the interval between two cancers was less than or equal to 6 months; and (7) exclude patients whose pathological type of SPM is not pancreatic ductal adenocarcinoma (n = 2,126). To screen out samples that fit clinicopathological types, we first used the International Classification of Neoplastic Diseases to select topographic codes with primary sites located in the pancreas (ICD-O-3: C25.0–C25.3, C25.7–C25.9) (19). Second, samples with ICD-O-3 histology/behavior code 8140/3 (adenocarcinoma) or 8500/3 (invasive ductal adenocarcinoma) were selected (19–21). The detailed process of data screening is shown in **Figure 1**. After removing samples with unknown data from the 67,945 samples in group B (race unknown, n = 129; surgical status unknown, n = 441; survival time unknown, n = 113), the remaining 67,262 samples were used for follow-up studies.

Statistical analysis

Numbers, percentage values, medians, quartiles, means, and variances were used to describe extreme baseline data. Survival differences between spPDAC and pPDAC samples were compared using KM survival curves and log-rank tests. All spPDAC samples were divided into a training set (n = 3,807) and a validation set (n = 1,632) according to the ratio of 7:3. The chi-square test was used to verify whether there were differences between categorical variables in the training and validation sets. Two independent sample t-tests were used to verify whether there was a difference in the interval between two primary cancers in the training and validation sets.

Causes of death were divided into pancreatic ductal adenocarcinoma-specific death (PDACSD) and death from other causes (DFOC). However, DFOC includes deaths from the first primary cancer. For the two events, PDACSD and DFOC, since one occurs, the other will not occur, so DFOC is an important competing event for PDACSD.

The Fine and Gray proportional subdistributed hazard method was used to analyze risk factors for PDACSD and DFOC. Using the risk factors of PDACSD, a competing risk model was constructed to predict the probability of PDACSD occurring in 6 months, 1 year, and 2 years. The effects of individual factors on the probability of occurrence of PDACSD and DFOC were analyzed by the univariate Fine–Gray test using the cumulative incidence function (CIF) (22, 23). The concordance index (C-index), the area under the curve (AUC), and the calibration curve were used to verify the accuracy and discrimination of the model. Decision curve analysis (DCA) (24) was used to analyze the benefit of patients after using the model.

All data analyses in this study were performed in R (version R-4.1.3). The "survival" and "survminer" packages were used for KM analysis and the log-rank test. The "chisq.test" package was used for chi-square tests. The "t.test" package was used for two independent sample t-tests. In the "cmprsk" package, the "crr()" function was used for the multivariate analysis of competing risk models, and the "cuminc()" function was used for the univariate Fine–Gray test. Packages "mstate," "rms," and "regplot" were used to draw competing risk nomograms. The "timeROC" and "survivalROC" packages were used to draw the area under the receiver operating characteristic curve. The "calPlot" package was used to draw calibration curves in competing risk models. The "Stdca" package is used to draw DCA (24). In all statistical tests in this paper, a two-sided p value less than 0.05 was considered statistically different.

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. Institutional review board approval was waived for this study because the SEER database is a public anonymized database. All of the methods we used in this study were carried out in accordance with relevant guidelines and regulations.

Results

Baseline characteristics of the study population

After a series of screening, 5,439 spPDAC samples and 67,262 pPDAC samples were finally included in the study. As shown in **Table 1**, spPDAC and pPDAC samples differed significantly in terms of gender, age, race, and marital status. Compared with spPDAC, pPDAC samples were younger and had more females. In addition, the TNM stage was relatively high in pPDAC samples. The baseline characteristics of the spPDAC sample are shown in **Table 2**, and the median (interquartile range, IQR)

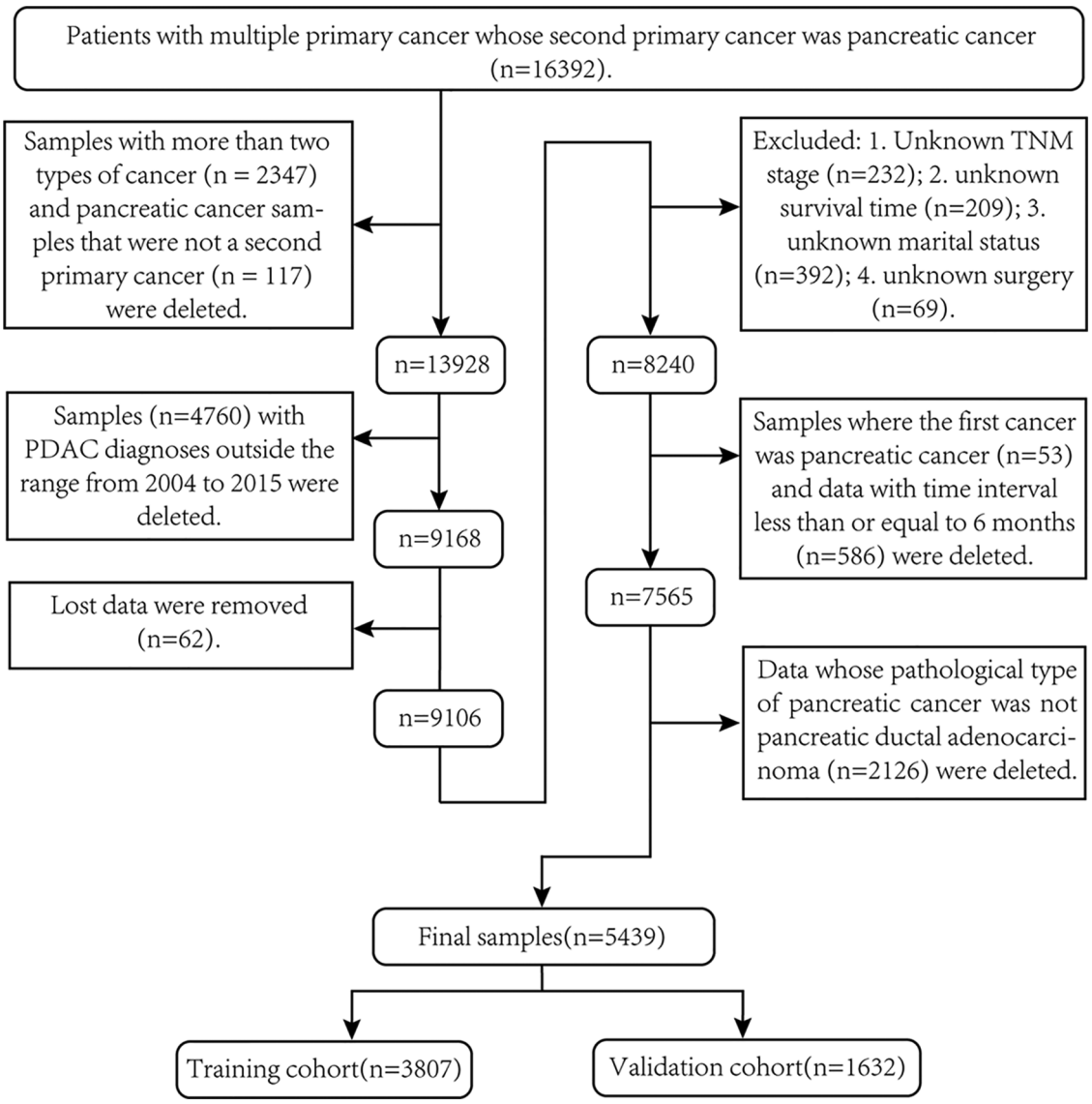

FIGURE 1
Screening process for second primary pancreatic ductal adenocarcinoma samples required for this study.

values of time to diagnosis for FPC and spPDAC were 2005 (2003, 2008) and 2011 (2008, 2014), respectively. The median ages at diagnosis for FPC and spPDAC were 68 (61, 75) and 73 (66, 80) years, respectively. The mean ages at diagnosis of FPC and spPDAC were 67.45 (9.81) and 72.67 (9.64) years, respectively. The median (IQR) of the time interval between the diagnosis of two primary cancers was 55 (28, 89) months, and the mean (standard deviation, SD) was 62.61 (41.15) months. The median (IQR) from spPDAC diagnosis to endpoint, competing event, or end of the study was 5 (2, 13) months. More than half of the patients (61.37%) used chemotherapy after the diagnosis of spPDAC. Only a small number of patients underwent surgery (18.75%) and radiotherapy (17.26%).

As shown in **Figure 2**, the three sites with the most FPCs were the prostate ($n = 1{,}685$), breast ($n = 948$), and digestive system ($n = 826$).

Influence of previous cancer history on prognosis

At the end of follow-up (time = 3 years), 5,127 patients in the spPDAC group had died, accounting for 94.26% of the total study sample. In the pPDAC subgroup, 63,050 samples died at the end of follow-up, accounting for 93.74% of the total sample. As shown, we plotted KM survival curves and validated them using the log-

TABLE 1 Demographic characteristics of patients.

	spPDAC ($n = 5,439$), n (%)	pPDAC ($n = 67,262$), n (%)	p
Sex, n (%)			<0.001
Female	2,212 (40.67)	32,662 (48.56)	
Male	3,227 (59.33)	34,600 (51.44)	
Age, year, n (%)			<0.001
<65	1,105 (20.31)	29,018 (43.14)	
≥65	4,334 (79.68)	38,244 (56.86)	
Race, n (%)			<0.001
White	4,476 (82.29)	53,440 (79.39)	
Black	643 (11.82)	8,455 (12.57)	
Other	320 (5.89)	5,367 (8.00)	
Marital status, n (%)			<0.001
Unmarried	2,065 (37.97)	30,017 (44.63)	
Married	3,374 (62.03)	37,245 (55.37)	
Site, n (%)			0.7347
PancreasHead	2,804 (51.55)	34,786 (51.72)	
PancreasBodyTail	1,354 (24.89)	16,934 (25.18)	
OthPancreas	1,281 (23.55)	15,542 (23.11)	
T stage, n (%)			<0.001
TX/1/2	2,437 (44.81)	28,063 (41.72)	
T3/4	3,002 (55.19)	39,199 (58.28)	
N stage, n (%)			<0.001
NX/0	3,702 (68.06)	43,882 (65.24)	
N1	1,737 (31.94)	23,380 (34.76)	
M stage, n (%)			<0.001
MX/0	2,849 (52.38)	32,531 (48.36)	
M1	2,590 (47.62)	34,731 (51.64)	
Surgery, n (%)			0.8882
Yes	1,020 (18.75)	12,562 (18.68)	
No	4,419 (81.25)	54,700 (81.32)	
Chemotherapy, n (%)			<0.001
Yes	2,794 (51.37)	36,896 (54.85)	
No	2,645 (48.63)	30,366 (45.15)	
Radiotherapy, n (%)			0.0151
Yes	939 (17.26)	12,507 (18.59)	
No	4,500 (82.74)	54,755 (81.41)	

TNM stage based on 6th edition staging of the American Joint Commission on Cancer.

rank test (Figure 3). The results showed that patients without a history of cancer had a better prognosis ($p = 0.0017$).

Cause of death analysis of spPDAC subgroups

As shown in Figure 4, 4,239 patients died from spPDAC, leaving 888 patients from FPC or other causes. As can be

TABLE 2 Overview of demographic and clinical factors in spPDAC patients.

At prior cancer diagnosis ($n = 5,439$)		At spPDAC diagnosis, ($n = 5,439$)	
Variables	**Value**	**Variables**	**Value**
Year of diagnosis		Year of diagnosis	
Median (IQR)	2005 (2003, 2008)	Median (IQR)	2011 (2008,2014)
Age, year		Age, year, n	
Mean (SD)	67.45 (9.81)	Mean (SD)	72.67 (9.64)
Median (IQR)	68 (61, 75)	Median (IQR)	73 (66, 80)
Sex, n (%)		Sex, n (%)	
Female	2,212 (40.67)	Female	2,212 (40.67)
Male	3,227 (59.33)	Male	3,227 (59.33)
Race, n (%)		Race, n (%)	
White	4,476 (82.29)	White	4,476 (82.29)
Black	643 (11.82)	Black	643 (11.82)
Other	320 (5.89)	Other	320 (5.89)
Marital status, n (%)		Marital status, n (%)	
Unmarried	1,702 (31.29)	Unmarried	2,065 (37.97)
Married	3,335 (61.32)	Married	3,374 (62.03)
Unknown	402 (7.39)	Unknown	~
T stage, n (%)		Site, n (%)	
TX\1\2	2,689 (49.44)	PancreasHead	2,804 (51.55)
T3\4	533 (9.80)	PancreasBodyTail	1,354 (24.89)
Unknown	2,217 (40.76)	OthPancreas	1,281 (23.55)
N stage, n (%)		T stage, n (%)	
NX\0	3,194 (58.72)	TX\1\2	2,437 (44.81)
N1	28 (0.51)	T3\4	3,002 (55.19)
Unknown	2,217 (40.76)	N stage, n (%)	
M stage, n (%)		NX\0	3,702 (68.06)
MX\0	3,140 (57.73)	N1	1,737 (31.94)
M1	82 (1.51)	M stage, n (%)	
Unknow	2,217 (40.76)	MX\0	2,849 (52.38)
Surgery, n (%)		M1	2,590 (47.12)
Yes	3,901 (71.72)	Surgery, n (%)	
No	1,514 (27.84)	Yes	1,020 (18.75)
Unknow	24 (0.44)	No	4,419 (81.25)
Chemotherapy, n (%)		Chemotherapy, n (%)	
Yes	992 (18.24)	Yes	2,794 (51.37)
No	4,447 (81.76)	No	2,645 (48.63)
Radiotherapy, n (%)		Radiotherapy, n (%)	
Yes	1,774 (32.62)	Yes	939 (17.26)
No	3,665 (67.38)	No	4,500 (82.74)
Interval between diagnoses, months		Time from spPDAC diagnosis to death or end of study, months	
Mean (SD)	62.61 (41.15)	Mean (SD)	9.09 (10.23)
Median (IQR)	55 (28, 89)	Median (IQR)	5 (2, 13)

Data were n (%)unless otherwise specified. IQR, interquartile range; spPDAC, Second primary pancreatic ductal adenocarcinoma; SD, standard deviation; ~, Not detectable.

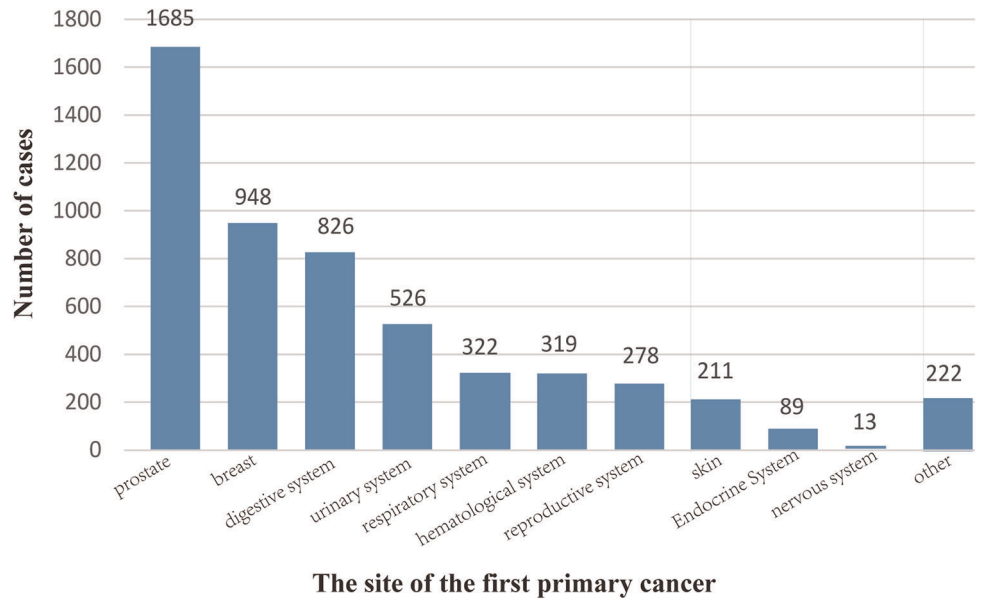

FIGURE 2
Location of the first primary cancer. We divided it into 11 sites, the most common of which is the prostate (1685), followed by the breast (948) and the digestive system (826). The locations of 5,439 cases are shown here.

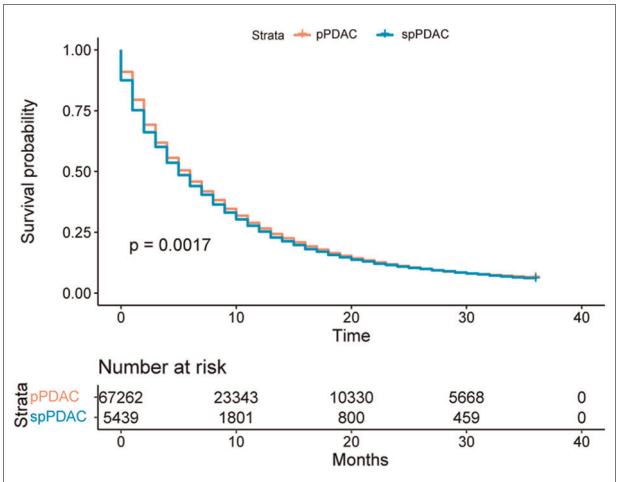

FIGURE 3
KM curve analysis of the difference in prognosis between spPDAC and pPDAC samples.

seen from the figure, spPDAC was the leading cause of death in spPDAC patients regardless of the location of the FPC. Compared with other systems, the respiratory system, digestive system, and urinary system had lower PDACSD, accounting for 72.08%, 76.84%, and 79.64%, respectively. The proportion of PDACSD in other parts was more than 80%.

Baseline characteristics of the training set and validation set

In a 7:3 ratio, the total study spPDAC sample ($n = 5,439$) was randomly divided into a training set ($n = 3,807$) and a validation set ($n = 1,632$). As shown in **Table 3**, gender, age, race, marital status, location of spPDAC, TNM stage, surgical treatment, chemotherapy, and the time interval between two primary cancers were not statistically different in the training set and validation set. The training set was used for the development and internal validation of the competing risk model. The validation set was used for external validation of the model. In the training cohort, there were more males, accounting for 59.50%, and the majority were elderly, accounting for 79.96%. More than half of the patients (51.12%) had spPDAC in the head of the pancreas. Most of the patients did not undergo surgery (81.46%) and radiotherapy (83.43%) after the diagnosis of spPDAC. About half of the patients (51.04%) used chemotherapy.

Competitive risk analysis

We divided the causes of death into PDACSD and DFOC and used the Fine and Gray proportional subdistributed hazard method to analyze the risk factors for death of

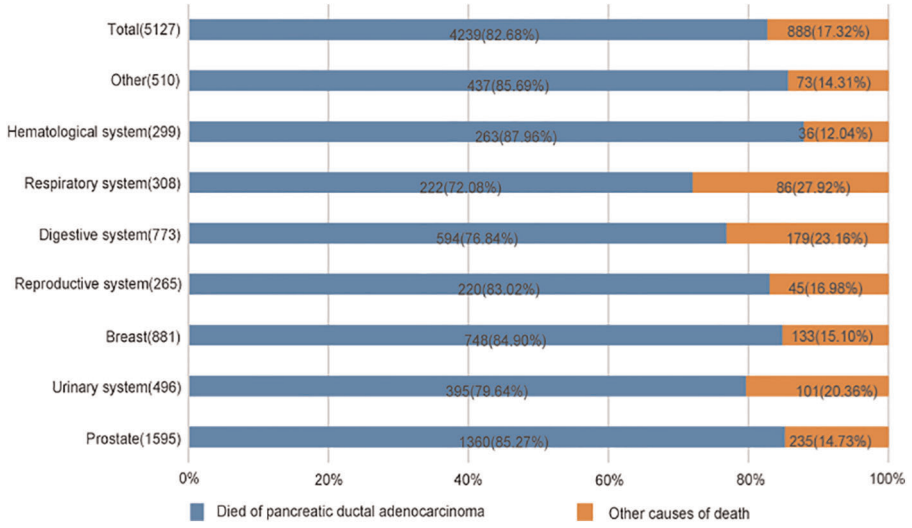

FIGURE 4
Percentage of spPDAC cancer-specific and other-cause-specific deaths, by location of first primary cancer. Compare the proportions of causes of death in this graph.

patients (Table 4). Age ($p < 0.001$), race ($p = 0.006$), interval ($p = 0.016$), location ($p < 0.001$), T stage ($p = 0.003$), M stage ($p < 0.001$), chemotherapy ($p < 0.001$), and radiotherapy ($p = 0.006$) were risk factors for PDACSD. From Table 4, we can find that patients who were older at diagnosis [subdistribution hazard ratio (sdHR) 1.225 (95% CI, 1.121–1.338)] were more likely to develop PDACSD. The higher the clinical T (sdHR = 1.130, 95% CI, 1.043–1.224) and M (sdHR = 1.279, 95% CI, 1.172–1.397) stage, the higher the probability of PDACSD. Compared with no chemotherapy or radiotherapy, chemotherapy (sdHR = 0.733, 95% CI, 0.678–0.793) and radiotherapy (sdHR = 0.888, 95% CI, 0.810–0.973) could significantly reduce the incidence of PDACSD. Compared with White, black (sdHR = 0.818, 95% CI, 0.720–0.929) and other skin-colored races (sdHR = 0.888, 95% CI, 0.758–1.040) were less likely to develop PDACSD. The longer the interval between FPC diagnosis and spPDAC (sdHR = 1.001, 95% CI, 1.000–1.002), the higher the probability of PDACSD.

Similarly, gender ($p = 0.023$), age ($p = 0.010$), race ($p = 0.004$), time interval ($p < 0.001$), specific location of spPDAC ($p < 0.001$), T stage ($p < 0.001$), and chemotherapy ($p < 0.001$) were associated with the occurrence of DFOC. DFOC includes not only deaths due to FPC but also other causes of death such as car accidents and cardiovascular disease.

The univariate Fine–Gray test showed that the cumulative probability of occurrence of PDACSD and DFOC showed significant differences when the values of individual clinical variables were different (Figure 5).

Development and validation of a pancreatic ductal adenocarcinoma-specific mortality nomogram

To make the model more practical in clinical practice, we developed a nomogram of competing risk models. In our nomogram, there are eight clinical variables, including age, the specific site of spPDAC occurrence, interval, T stage, M stage, surgery, chemotherapy, and radiotherapy (Figure 6). The probability of occurrence of PDACSD in 6 months, 1 year, and 2 years can be predicted only by adding the scores of each variable of spPDAC patients. We used the C-index to verify the accuracy of the model. The C-index values were 0.665 (95% CI, 0.655, 0.675) and 0.666 (95% CI, 0.650, 0.682) for the training and validation sets, respectively. This showed that the model has a better discriminative ability. The training set and validation set AUC showed that our model has good discrimination (Figures 7A,B). The calibration curves showed that the predicted and actual observed values of the model were almost consistent (Figures 7C,D). DCA (Figures 7E–J) showed that the model had good clinical utility in predicting 6-month, 1-year, and 2-year PDACSD.

Discussion

In this study, we first analyzed the impact of previous cancer history on the prognosis of patients with PDAC. The results suggest that PDAC patients without a previous history of

TABLE 3 Demographics of training and validation sets.

	Total (n = 5,439), n (%)	Training set (n = 3,807), n (%)	Validation set (n = 1,632), n (%)	p
Sex, n (%)				0.7053
Female	2,212 (40.67)	1,542 (40.50)	670 (41.05)	
Male	3,227 (59.33)	2,265 (59.50)	962 (58.95)	
Age, year, n (%)				0.4427
<65	1,105 (20.31)	763 (20.04)	342 (20.96)	
≥65	4,334 (79.68)	3,044 (79.96)	1,290 (79.04)	
Race, n (%)				0.9611
White	4,476 (82.29)	3,136 (82.37)	1,340 (82.11)	
Black	643 (11.82)	447 (11.74)	196 (12.01)	
Other	320 (5.89)	224 (5.88)	96 (5.88)	
Marital status, n (%)				0.1500
Unmarried	2,065 (37.97)	1,469 (38.59)	596 (36.52)	
Married	3,374 (62.03)	2,338 (61.41)	1,036 (63.48)	
Interval, month				0.9643
Mean (SD)	62.61 (41.15)	62.63 (41.06)	62.58 (41.36)	
Median (IQR)	55 (28, 89)	55 (28,88)	55 (28,89)	
Site, n (%)				0.0804
PancreasHead	2,804 (51.55)	1,946 (51.12)	858 (52.57)	
PancreasBodyTail	1,354 (24.89)	980 (25.74)	374 (22.92)	
OthPancreas	1,281 (23.55)	881 (23.14)	400 (24.51)	
T stage, n (%)				0.9889
TX/1/2	2,437 (44.81)	1,706 (44.81)	731 (44.79)	
T3/4	3,002 (55.19)	2,101 (55.19)	901 (55.21)	
N stage, n (%)				0.4390
NX/0	3,702 (68.06)	2,579 (67.74)	1,123 (68.81)	
N1	1,737 (31.94)	1,228 (32.26)	509 (31.19)	
M stage, n (%)				0.2327
MX/0	2,849 (52.38)	1,974 (51.85)	875 (53.62)	
M1	2,590 (47.62)	1,833 (48.15)	757 (46.38)	
Surgery, n (%)				0.5471
Yes	1,020 (18.75)	706 (18.54)	314 (19.24)	
No	4,419 (81.25)	3,101 (81.46)	1,318 (80.76)	
Chemotherapy, n (%)				0.4541
Yes	2,794 (51.37)	1,943 (51.04)	851 (52.14)	
No	2,645 (48.63)	1,864 (48.96)	781 (47.86)	
Radiotherapy, n (%)				0.0399
Yes	939 (17.26)	631 (16.57)	308 (18.87)	
No	4,500 (82.74)	3,176 (83.43)	1,324 (81.13)	

TNM stage based on 6th edition staging of American Joint Commission on Cancer.

TABLE 4 Competing risk models for mortality from pancreatic ductal adenocarcinoma and death from other causes.

Characteristics	Death from spPDAC		Death from other causes	
	sdHR (95%CI)	p	sdHR (95%CI)	p
Sex		0.780		0.023
Female	Reference		Reference	
Male	0.994 (0.920–1.074)	0.880	1.192 (1.001–1.418)	0.048
Age		<0.001		0.010
<65	Reference		Reference	
≥65	1.225 (1.121–1.338)	<0.001	0.786 (0.646–0.955)	0.015
Race		0.006		0.004
White	Reference		Reference	
Black	0.818 (0.720–0.929)	0.002	1.660 (1.347–2.046)	<0.001
Other	0.888 (0.758–1.040)	0.140	1.085 (0.772–1.526)	0.640
Marital status		0.950		0.054
Unmarried	Reference		Reference	
Married	0.991 (0.913–1.075)	0.820	0.887 (0.747–1.055)	0.180
Interval	1.001 (1.000–1.002)	0.016	0.997 (0.995–0.999)	0.005
Site		<0.001		<0.001
PancreasHead	Reference		Reference	
PancreasBodyTail	1.006 (0.921–1.099)	0.890	1.023 (0.834–1.256)	0.830
OthPancreas	0.817 (0.738–0.905)	<0.001	1.526 (1.260–1.849)	<0.001
T stage		0.003		<0.001
TX/1/2	Reference		Reference	
T3/4	1.130 (1.043–1.224)	0.003	0.698 (0.587–0.830)	<0.001
N stage		0.280		0.660
NX/0	Reference		Reference	
N1	1.051 (0.968–1.141)	0.240	1.035 (0.860–1.246)	0.710
M stage		<0.001		0.760
MX/0	Reference		Reference	
M1	1.279 (1.172–1.397)	<0.001	0.981 (0.817–1.179)	0.840
Surgery		0.000		0.840
No	Reference		Reference	
Yes	0.518 (0.469–0.573)	0.000	1.010 (0.792–1.287)	0.940
Chemotherapy		<0.001		<0.001
No	Reference		Reference	
Yes	0.733 (0.678–0.793)	<0.001	0.593 (0.496–0.709)	<0.001
Radiotherapy		0.006		0.310
No	Reference		Reference	
Yes	0.888 (0.810–0.973)	0.011	1.101 (0.866–1.401)	0.430

sdHR, subdistribution hazard ratio; CI, confidence interval; TNM stage based on the 6th edition staging of the American Joint Commission on Cancer (AJCC); spPDAC, second primary pancreatic ductal adenocarcinoma.

cancer have a better prognosis. The difference in prognosis between the spPDAC subgroup and the pPDAC subgroup also implies that previous studies on the prognostic characteristics of the pPDAC patient population were not applicable to the spPDAC population. Therefore, developing a prediction model suitable for the spPDAC population is of great significance for the precise treatment of spPDAC.

We used the Fine and Gray proportional subdistributed hazard method to identify risk factors significantly associated

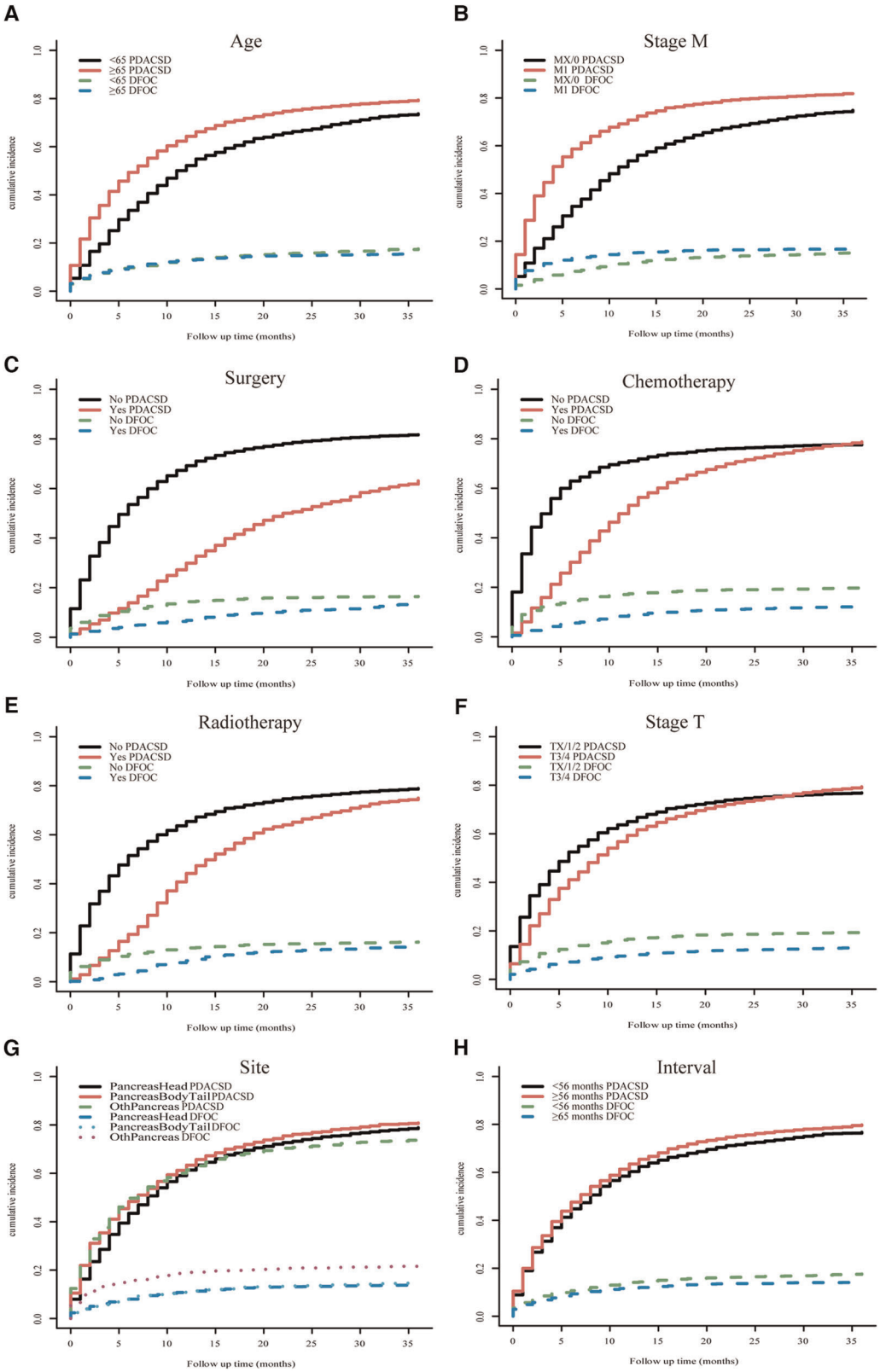

FIGURE 5
Univariate Fine–Gray test was used to analyze the cumulative incidence of pancreatic ductal adenocarcinoma-specific death and death from other causes. Age (A), M stage (B), surgery (C), chemotherapy (D), radiotherapy (E), T stage (F), location (G), and time interval (H).

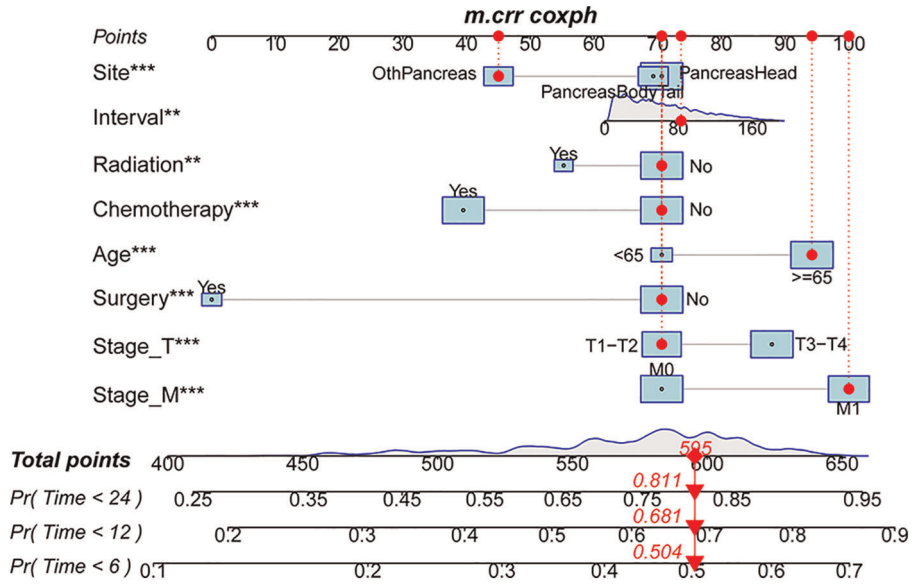

FIGURE 6
Nomogram for predicting 6-month, 1-year, and 2-year pancreatic ductal adenocarcinoma-specific mortality in patients with second primary pancreatic ductal adenocarcinoma.

with PDACSD, including age, race, interval, location, T stage, M stage, chemotherapy, and radiotherapy. We constructed a competing risk model nomogram to assess the probability of developing PDACSD in spPDAC patients.

We identified the three most common FPCs in spPDAC patients followed by prostate cancer, breast cancer, and digestive malignancies. Similar to our conclusions, He et al. (25) found in a retrospective study that the most common sites of previous cancer in spPDAC patients were the prostate, breast, kidney, and bladder. Prostate cancer is the most common site, probably because of its higher incidence and better prognosis (26, 27). These key populations should be carefully screened.

Jo et al. (28) conducted a retrospective cohort study and found that the mean age of patients with spPDAC ($n = 110$) was significantly higher (66.5 vs. 62.2 years) compared with pPDAC patients ($n = 1{,}606$, $p < 0.001$). In our study, age was an important risk factor for developing PDACSD in spPDAC patients ($p < 0.001$). In all spPDAC samples, the mean age (SD) of patients was 72.67 (9.64) years old. In the training set, patients 65 years or older had a higher risk of developing PDACSD (sdHR = 1.225, 95% CI, 1.121–1.338). Studies have shown that there are significant differences in the treatment decisions and clinical prognosis of PDAC with different ages, and PDAC is age-dependent cancer (29). Age is considered an independent prognostic factor for PDAC (29, 30).

PDAC has always been a very malignant tumor. In the United States, PDAC is the third leading cause of cancer-related death (31). Due to the highly aggressive nature of PDAC, patients often have local invasion and distant metastasis at the time of diagnosis, resulting in poor prognosis in PDAC patients (32). According to research statistics, the average survival time after PDAC diagnosis is only 6–9 months (33–35). At the end of our 3-year follow-up, 94.26% of patients had died, including 82.68% of PDACSD. This also supports the characteristics of high malignancy and poor prognosis of PDAC.

The treatment methods of PDAC mainly include surgery, chemotherapy, radiation therapy, immunotherapy, and targeted therapy. Radical surgical resection is the most effective method for PDAC (36), but only 20% of patients achieve effective remission with surgical treatment (37). At present, there is no authoritative organization to formulate surgical treatment standards for spPDAC. Doctors often judge whether a patient can undergo surgical treatment according to the patient's physical condition and tumor progression, combined with the surgical treatment standards for PDAC(38–40). Therefore, for the special group of spPDAC, more research and authoritative diagnosis and treatment standards are urgently needed. Standard FOLFIRINOX or gemcitabine-based combination chemotherapy can slightly improve overall survival, but most patients die from disease progression (41–43). In recent years, preoperative neoadjuvant therapy for PDAC has gained wide acceptance (44–46). Studies have reported that preoperative neoadjuvant radiotherapy and chemotherapy can improve the resectability of locally advanced PDAC (47, 48). In this study, patients who underwent surgery, chemotherapy, and radiotherapy had a relatively lower probability of PDACSD, and their sdHR (95% CI) values were 0.518 (0.469–0.573), 0.733 (0.678–0.793), and 0.888 (0.810–0.973), respectively. Targeted

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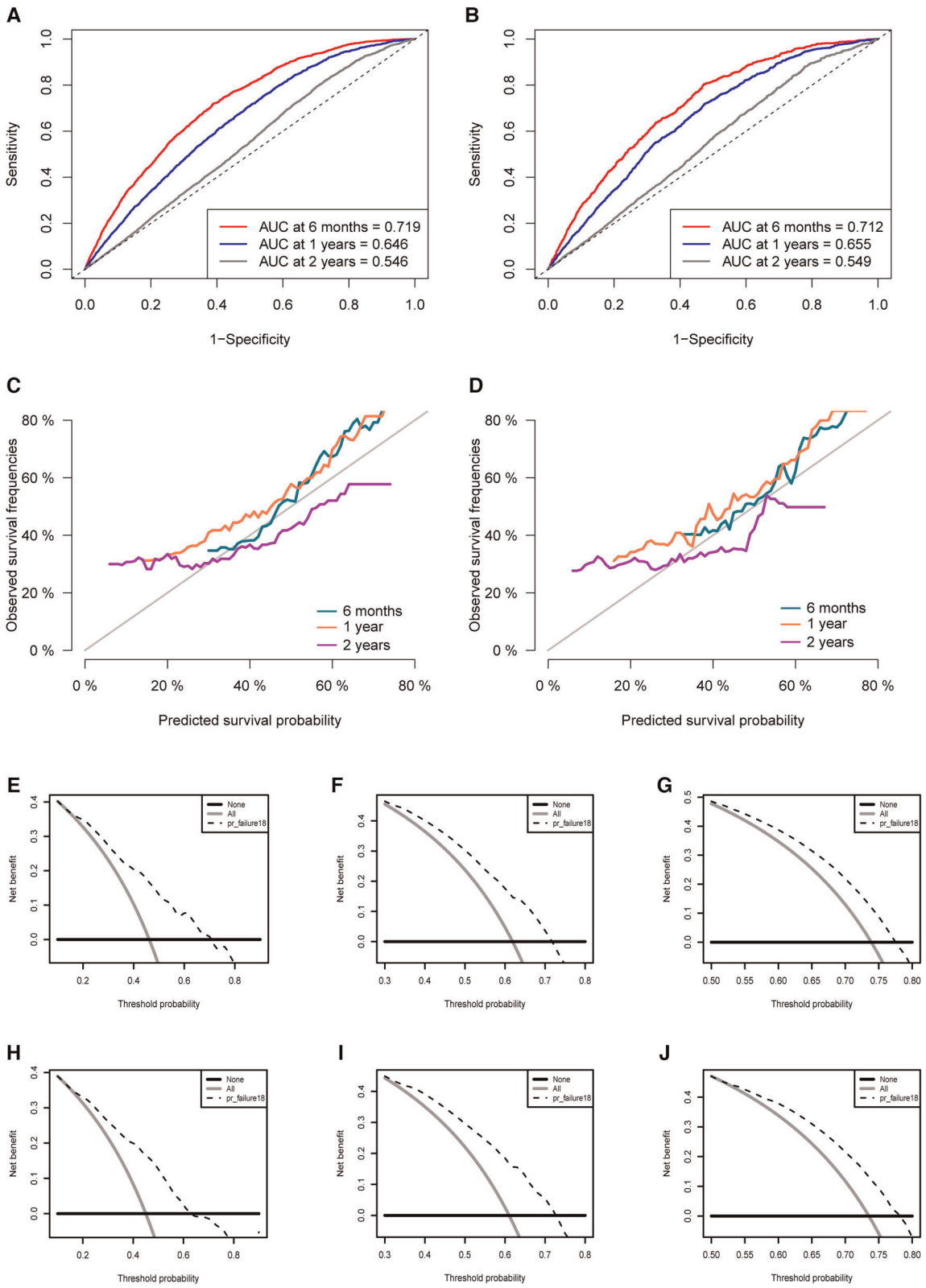

FIGURE 7
Area under the receiver operating characteristic curve for the training set (A) and validation set (B). Calibration curves in the training set (C) and validation set (D). Decision curves for half a year (E), 1 year (F), 2 years (G) in the training set. Decision curves for half a year (H), 1 year (I), 2 years (J) in the validation set.

therapy has developed rapidly in the treatment of breast and ovarian cancer, enabling treatment in a precise manner (49, 50). However, for PDAC, targeted therapy has been slow to develop, and the only approved precision therapy drug, erlotinib, has only marginally improved survival (51, 52). Not only that, but immunotherapy has a limited role in PDAC (53). Humans still have a long way to go in the treatment of PDAC.

The median time interval (IQR) between diagnosis of FPC and spPDAC was 55 (28, 89) months. To avoid the possibility of synchronous transfer, we only selected samples with time intervals greater than 6 months for study. The shortest and longest intervals were 7 months and 180 months, respectively. Our study found that the longer the interval (month), the higher the risk of developing PDACSD in spPDAC patients ($p = 0.016$).

Due to the lack of reliable criteria for evaluating spPDAC, clinicians often make empirical judgments based on imaging studies, TNM staging, and the patient's physical condition (54, 55). Through multivariate Cox regression analysis, He and his colleagues (25) identified age ($p < 0.001$), sex ($p < 0.001$), race ($p < 0.001$), tumor size ($p < 0.001$), prior history of cancer ($p < 0.001$), SEER stage ($p < 0.001$), grade ($p < 0.001$), surgery ($p < 0.001$), chemotherapy ($p < 0.001$), and radiotherapy ($p < 0.001$) were the risk factors affecting the overall survival of patients. In competing risk events, He et al. used traditional analytical methods (Cox regression analysis and Kaplan–Meier analysis), which tended to overestimate the probability of PDACSD, creating a competing risk bias. This kind of research bias is not uncommon, and one study found that this error may occur in 46% of the literature (22). Patients with spPDAC may die from other causes such as traffic accidents and cardiovascular disease. For these causes of death, spPDAC did not contribute, and these causes of death could not be combined with PDACSD to analyze risk factors for spPDAC. Therefore, in competing risk events, the Fine and Gray proportional sub-distributed hazard method is advocated (56, 57). To the best of our knowledge, researchers have used the Fine and Gray proportional subdistributed hazard method to construct competing risk models for multiple primary cancers associated with cervical cancer (58) and colorectal cancer (59). However, competing risk models for spPDAC cancer-specific mortality have not yet emerged. Hopefully, our results can fill this gap.

Although we investigated risk factors associated with PDACSD and established a good prognostic prediction model for spPDAC, there are inevitably some deficiencies. First, this is a retrospective study, and some selection differences cannot be avoided, which may lead to specific biases. Second, the SEER database lacks some key information related to PDACSD, such as smoking, alcohol consumption, obesity, type II diabetes, tumor markers, surgical methods, chemoradiotherapy regimens, immunotherapy, and so on. (60–62). This prevents us from analyzing patient information comprehensively. Finally, our model needs to be validated in a large-scale prospective study.

Conclusions

In conclusion, we analyzed the impact of previous cancer on the prognosis of spPDAC, screened risk factors for PDACSD in spPDAC patients, and constructed a competing risk model. The model has good accuracy and discriminative ability, which can assist doctors and patients in clinical decision-making.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: All data used in this work can be acquired from the SEER database (SEER: https://seer.cancer.gov/). To download SEER*Stat, visit http://seer.cancer.gov/seerstat/download. The author Lishan Song has gotten access to the SEER database (accession number:23514-Nov2020). Select the following datasets: Incidence - SEER Research Plus Data, 18 Registries (excl AK), Nov 2020 Sub (2000–2018)—Linked To County Attributes—Total US, 1969–2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission.

Author contributions

LS, CX, TZ, and XL contributed to the conception and design of the study. LS and CX organized the database. LS, CX, ZS, and SH performed the statistical analysis. LS wrote the first draft of the manuscript. LS, BC, HT, GW and SC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

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Prognostic role of the prognostic nutritional index in patients with pancreatic cancer who underwent curative resection without preoperative neoadjuvant treatment: A systematic review and meta-analysis

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Background: The prognostic nutrition index (PNI), which has been evaluated in various kinds of cancers, offered a simple yet effective approach to predict the prognosis. The aim of this meta-analysis is to reveal the correlation between preoperative PNI and the prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) who underwent curative resection.

Methods: We searched the PubMed, Embase, Web of Science and Cochrane Library databases, and extracted the hazard ratio (HR) with 95% confidential interval (CI) from eligible studies. The pooled HR with 95% CI was applied to evaluate the association between PNI and overall survival (OS), recurrence-free survival (RFS).

Results: A total of fourteen studies with 3,385 patients were included for meta-analysis. The results (the pooled HR: 1.664, 95% CI: 1.424–1.994, $I^2 = 42.6\%$, p value = 0.046) indicated that low preoperative PNI was closely related to poor OS. In addition, the results suggested that PNI was negatively correlated with RFS (the pooled HR: 1.369, 95%CI: 1.080–1.734). The robustness of these pooled results was verified by our subgroup analysis and sensitivity analysis. Moreover, different cutoff values among studies are responsible for the heterogeneity of pooled HR of OS through meta-regression analysis (p value = 0.042). Funnel plots, Begg's test (p value = 0.228) and Egger's test (p value = 0.702) indicated no significant publication bias in OS.

Conclusion: Preoperative PNI might be a promising marker to predict the prognosis of PDAC patients who underwent curative resection.

KEYWORDS

pancreatic cancer, meta-analysis, prognosis, surgery, prognostic nutritional index

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignant digestive system tumors with a 5-year survival rate of approximately 9% (1). Surgical resection is taken as the only curative therapy for PDAC, and the 5-year survival rate after radical resection is about 20% (2). Despite advancements in medical technology, the prognosis of PDAC is still very poor. Therefore, it is vital to identify a marker that can predict the prognosis for patients with PDAC.

An increasing number of studies have shown that inflammation and nutrition status play a significant role in oncogenesis, progression and metastasis (3–5). Inflammatory indices, such as neutrophil-to-lymphocyte ratio (NLR) (6), platelet-to-lymphocyte ratio (PLR) (7) and controlling nutritional status (CONUT) score (8), have been applied to predict the prognosis of patients with PDAC. Prognostic nutritional index (PNI) was initially reported by Buzby and colleagues in 1980, and it calculated as 158 − 16 (ALB) − 0.78 (TSF) − 0.20 (TFN) − 5.8 (DH). (ALB is serum albumin level (g/100 ml), TSF is triceps, skinfold (mm), TFN is serum transferrin level (mg/100 ml) and DH is delayed hypersensitivity reactivity to any of three recall antigens (mumps, streptokinase-streptodornase, candida) graded as 0, 1, 2) (9). Then in 1984, Onodera T. developed a relatively simple and convenient formula of PNI to assess the risk of postoperative complications and the prognosis of gastrointestinal cancer patients after surgery, which was $10 \times$ serum albumin (g/dl) $+ 0.005 \times$ total lymphocyte count (10). Subsequently, Onodera's PNI was widely utilized to predict the prognosis of various cancers since 2010s, including gastric cancer (11), hepatocellular cancer (12), lung cancer (13), colorectal cancer (14–16), etc. A few studies have investigated the relationship between the PNI and the prognosis of PDAC (17–19). The results of two previous meta-analysis studies indicated that low PNI was related to poorer OS. Nevertheless, they analyzed mixed patients who treated with surgery alone, chemotherapy/chemoradiotherapy alone or preoperative chemotherapy/chemoradiotherapy followed by surgery, which could bring about bias, and the conclusion might not be very reliable. These preoperative treatment regimes, especially the chemotherapy, may decline the lymphocyte count and albumin concentration *via* myelosuppression and chemotherapy toxicity, which could impact the calculation of PNI subsequently. Hence, our aim was to perform a systematic review and meta-analysis of the current published studies to evaluate the clinical significance of PNI as a preoperative prognostic factor in patient with PDAC underwent curative resection.

Materials and methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (20).

Search strategies

PubMed, Embase, Web of Science, and Cochrane Library databases were searched for eligible articles up to March 1st, 2022. The search was conducted using medical subject headings (MeSH) in combination with free text words. The search strategy in PubMed database was the following: ("Pancreatic Neoplasms" [MeSH Terms] OR (("Pancreatic" [Title/Abstract] OR "pancreas" [Title/Abstract]) AND ("adenocarcinoma" [Title/Abstract] OR "carcinoma" [Title/Abstract] OR "cancer" [Title/Abstract] OR "neoplasm*" [Title/Abstract] OR "tumor" [Title/Abstract]))) AND ("Prognostic Nutritional Index" "[Title/Abstract]" OR "Prognostic Nutritional Indices" "[Title/Abstract]" OR "PNI" [Title/Abstract]).

Inclusion and exclusion criteria

All studies included in the meta-analysis were selected according to the following inclusion criteria: (1) studies including patients who underwent curative surgical resection and confirmed as PDAC by histopathological or pathological analysis, (2) PNI was calculated using Onodera's simplified formula, and measured before surgery, (3) studies investigating the relationship between preoperative PNI and the prognosis of PDAC, (4) hazard ratio (HR) with 95% confidence interval (CI) or other necessary data was available, and (5) studies written in English and published in full-text. The exclusion criteria were as follows: (1) patients received any preoperative neoadjuvant chemotherapy, chemoradiotherapy, or immunotherapy, (2) abstracts, case reports, editorials, letters, systematic reviews, and comments, (3) studies with incomplete data, (4) studies enrolled the overlapped or same population, and (5) duplicate studies.

Data extraction

Two investigators (PCZ and ZWW) independently extracted necessary data from included studies and any disagreements were resolved by discussion till reach consensus. The following data were extracted from each study: first author, publication year, country, study design, age of the study population, male/female, sample size, cutoff value of PNI, tumor stage, duration of follow-up, operation, outcome measures, type of analysis, and recurrence-free survival (RFS) and overall survival (OS) with HR and their 95% CI. Because of confounding factor adjustment, the multivariate analysis was preferred when the HRs for OS or RFS were obtained using both univariate and multivariate analyses. If HR with 95% CI was not provided in original studies, we extracted from the survival curve by using Engauge Digitizer software (https://markummitchell.github.io/engauge-digitizer/).

Quality assessment

The Newcastle-Ottawa quality assessment Scale (NOS) was used to evaluate the quality of included studies. The NOS consists of 3 aspects: selection (4 points maximum), comparability (2 points maximum) and outcomes (3 points maximum). Studies with a score of six or higher were considered as high-quality studies (21). This work was also performed independently by our two investigators (PCZ and ZWW). (**Supplementary Table S1**)

Statistical analysis

Meta-analysis was conducted using Stata 14.0 software (https://www.stata.com/stata14/). The pooled HR with 95% CI was used to evaluate the relationship between the preoperative PNI and the outcome in patients with PDAC. The heterogeneity of pooled HR was accessed using Cochran's Q test and Higgins I^2 statistic. Q test p value < 0.1 or $I^2 > 50\%$ was considered significant heterogeneity and random-effect model was applied to estimate the pooled HR. While heterogeneity was not significant (Q test p value > 0.1 or $I^2 < 50\%$), a fixed-effect model was used. To reduce and explain the heterogeneity of OS among studies, subgroup analyses, meta-regression analysis and sensitivity analysis were applied. Furthermore, publication bias was visually checked through funnel plot, and then quantitatively analyzed by Begg's and Egger's tests. All statistical tests were two-sided, and p value less than 0.05 were defined as statistically significant.

Results

Study selection

We searched PubMed, Embase, Web of Science, and Cochrane Library databases, and a total of 868 articles were initially retrieved. After removing 309 duplicates, 559 articles remained. After screening the titles and abstracts, 455 articles were excluded for being irrelevant topics, reviews or meta-analysis, conference abstracts, or meeting. Among the remained 104 articles, only 55 articles were performed among patients who underwent curative resection. Finally, 14 articles met our inclusion criteria and 3,385 patients were included in this meta-analysis (17–19, 22–31). The detailed selection process was illustrated in **Figure 1**.

Clinical characteristic of enrolled studies

The main characteristics of included studies were presented in **Table 1**. These included studies were retrospective studies, and mainly published in the past ten years. All included

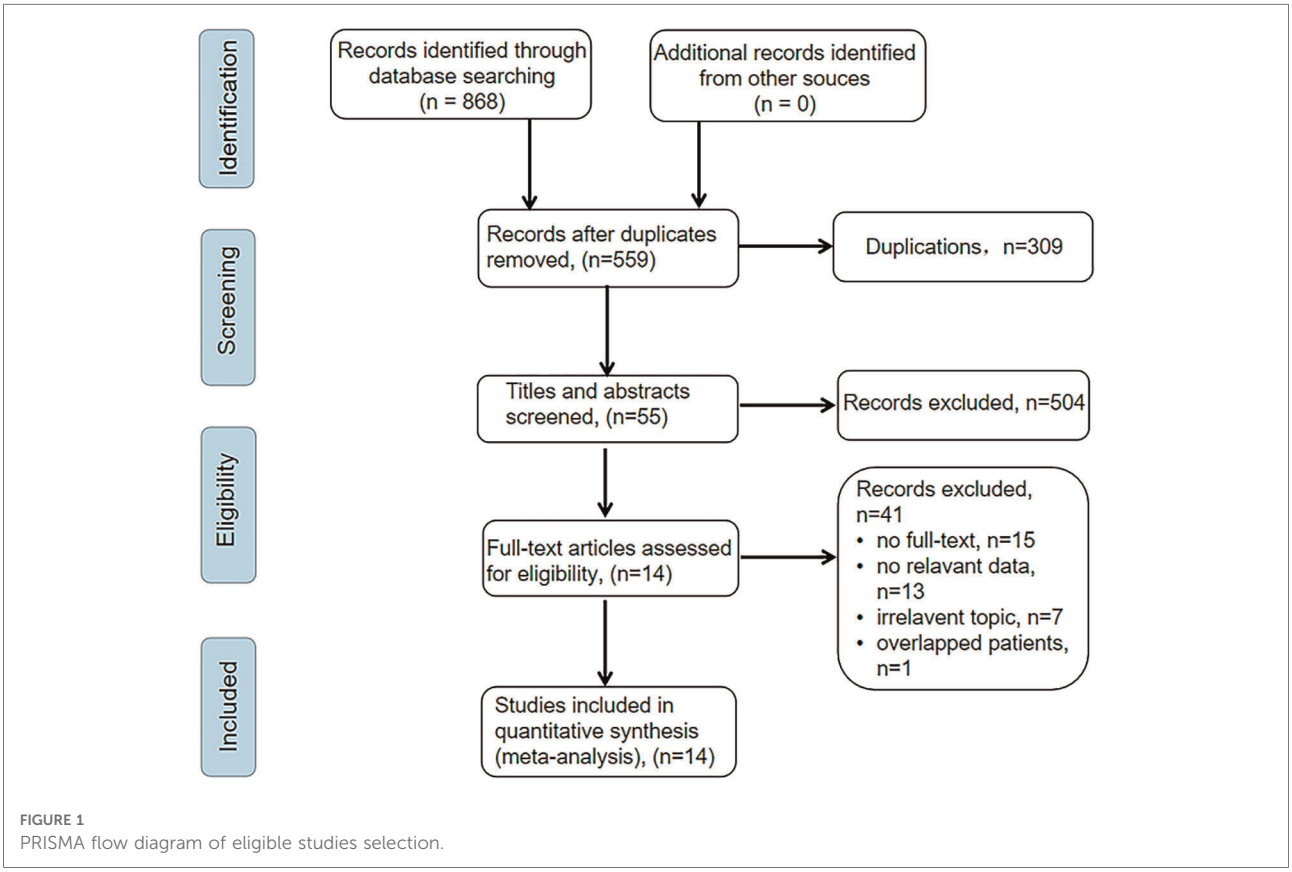

FIGURE 1
PRISMA flow diagram of eligible studies selection.

TABLE 1 The main characteristics of included studies.

Year	Author	Country	Study type	Sample size (low PNI/high PNI)	Tumor stage	Operation (PD/DP/MP/TP)	Median follow-up (months)	Cutoff value	Postoperative chemotherapy, *n*=	Analysis model	Outcome	NOS
2011	Kanda M.	Japan	R	74/194	I–IV	195/48/0/25	NA	45	NA	M	OS	6
2016	Asaoka T.	Japan	R	21/25	I–III	Only PD	NA	47	26	M	OS	6
2016	Watanabe J.	Japan	R	9/37	I–III	Only PD	NA	40	30	U	OS	6
2018	Abe T.	Japan	R	206/123	I–III	214/96/0/19	NA	45	286	M	OS	7
2019	Ikeguchi M.	Japan	R	24/26	I–III	33/15/0/2	NA	46	NA	M	OS	6
2019	Ikuta S.	Japan	R	90/46	I–IV	83/53/0/0	16.8	48.8	112	U	OS	8
2019	Onoe S.	Japan	R	18/147	I–III	Only PD	59.6	38	66	M	OS	7
2020	Hoshimoto S.	Japan	R	92/119	I–IV	119/80/0/12	19.0	47.25	113	U	OS	7
2020	Mao Y. S.	China	R	75/231	I–III	NA	NA	45	NA	M	OS	6
2020	Xu S. S.	China	R	333/249	I–III	243/339/0/0	NA	53.10	477	U	OS	7
2021	Abe T.	Japan	R	26/133	I–III	69/79/0/11	27.6	40	105	M	OS/RFS	7
2021	Itoh S.	Japan	R	256/333	I–III	394/179/0/16	NA	46	NA	M	OS/RFS	6
2021	Onoe S.	Japan	R	62/125	I–IV	125/40/0/22	39.8	36	147	M	OS	7
2021	Terasaki F.	Japan	R	122/185	I–IV	237/70/0/0	NA	50	219	M	OS	6

R, retrospective; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; MP, medial pancreatectomy; TP, total pancreatectomy; NA, not applicable; M, multivariate; U, univariate; OS, overall survival; RFS, recurrence-free survival; NOS, Newcastle–Ottawa scale.

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studies used the Onodera's PNI. Twelve of fourteen studies were from Japan, and two studies were from China. The sample size of enrolled studies varied from 46 to 589. In all selected articles, the correlation between PNI and OS was presented, while RFS was additionally analyzed in two studies. The preoperative PNI cut off value were not consistent ranged from 36 to 53.10. Multivariate analyses were conducted in ten of fourteenth studies. The scores of study quality assessed by NOS ranged from 6 to 8.

Relationship between PNI and OS

As illustrated in Figure 2, a total of 14 studies were enrolled in this meta-analysis, and the results indicated that patients with low PNI had significantly worse OS (HR = 1.664, 95%CI: 1.424–1.944, $I^2 = 42.6\%$, p value = 0.046). Subgroup analyses were conducted based on the sample size, tumor stage, cutoff value, and analysis model, and the results revealed that low PNI was still associated with inferior OS in all subgroups. Meta-regression analysis was performed to explore the heterogeneity, and the p value of cutoff value subgroup was 0.042, which indicated that using different cutoff value among studies might be the source of heterogeneity. Meanwhile, PNI was confirmed as an independent preoperative prognostic factor of OS in 6 studies (17–19, 23, 26, 28). All results of subgroup analyses and meta-regression analyses were shown in Table 2.

Relationship between PNI and RFS

Two studies reported the prognostic value of PNI for RFS (17, 24), the pooled results were: HR: 1.369, 95%CI: 1.080–1.734, $I^2 = 0$, p value = 0.689, which suggested patients with lower PNI had shorter RFS than those with high PNI (Figure 3).

Sensitivity analysis and publication bias

Sensitivity analysis was conducted to assess the effect of individual studies on the pooled HR of OS, and the result revealed that omitting any individual studies had no

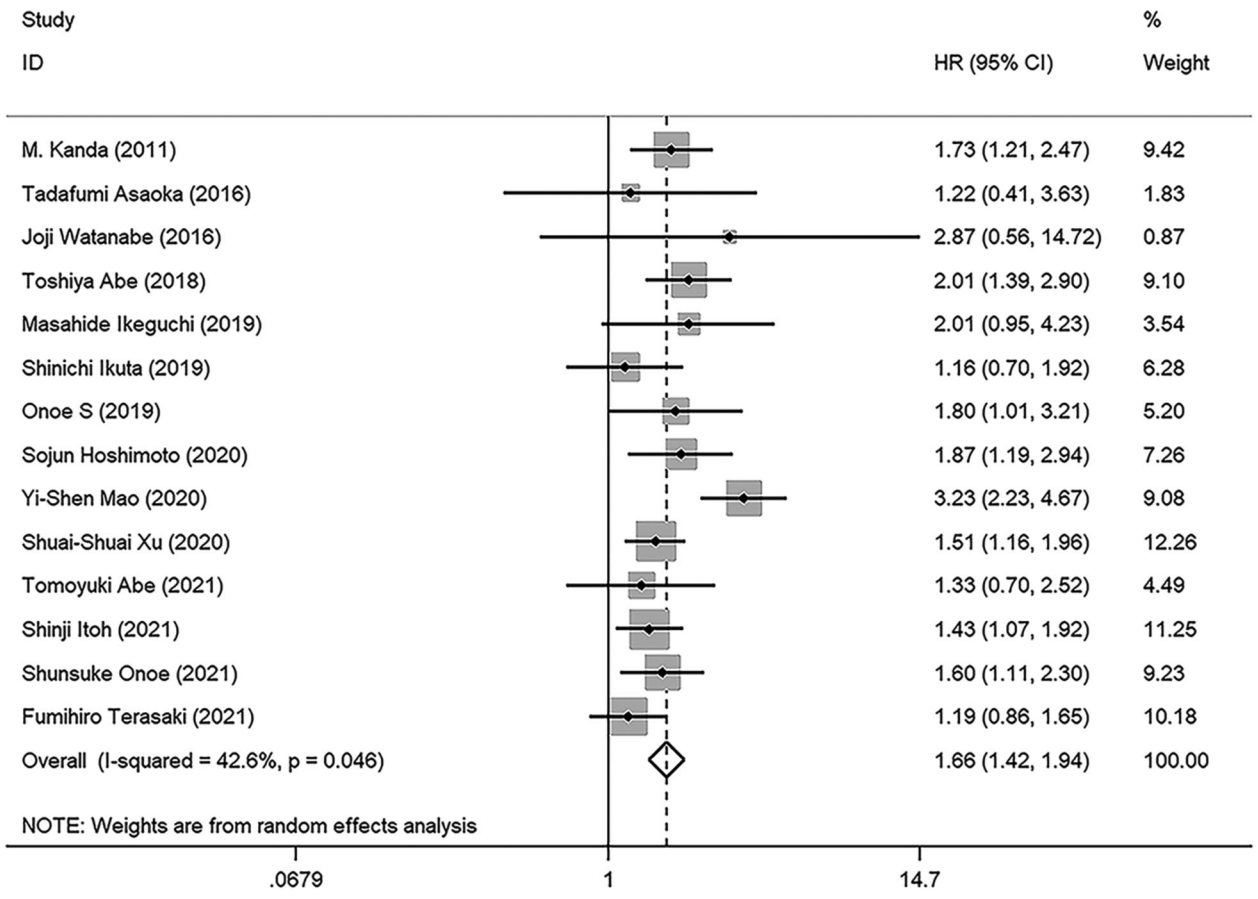

FIGURE 2
Forest plot of the association between PNI and OS. (OS, overall survival; HR, hazard ratio; CI, confidence interval).

TABLE 2 The results of subgroup analyses and meta-regression analyses.

Subgroup	References	Patients, *n*=	Random-effects model		Fixed-effects model		*p* value (heterogeneity)	I^2, %	*p* value (meta-regression)
			HR, 95%CI	*p* value	HR, 95%CI	*p* value			
Sample size									
≤200	(23, 24, 28–32)	793	1.524 (1.218–1.908)	<0.001	1.524 (1.218–1.908)	<0.001	0.814	0	0.502
>200	(17–19, 22, 25–27)	2592	1.742 (1.386–2.190)	<0.001	1.685 (1.486–1.911)	<0.001	0.004	68.6	
Tumor stage									
I–III	(17, 18, 24–26, 28, 30–32)	2276	1.812 (1.444–2.273)	<0.001	1.767 (1.533–2.037)	<0.001	0.047	49	0.257
I–IV	(19, 22, 23, 27, 29)	1109	1.482 (1.231–1.784)	<0.001	1.480 (1.245–1.759)	<0.001	0.336	12.2	
Cutoff value									
≤45	(18, 19, 23, 24, 26, 28, 31)	1464	1.952 (1.546–2.456)	<0.001	1.974 (1.670–2.333)	<0.001	0.111	42.0	0.042
>45	(17, 22, 25, 27, 29, 30, 32)	1921	1.432 (1.238–1.657)	<0.001	1.432 (1.238–1.657)	<0.001	0.638	0	
Analysis type									
Multivariate	(17–19, 22–24, 26, 28, 30, 32)	2410	1.714 (1.398–2.101)	<0.001	1.696 (1.489–1.932)	<0.001	0.022	53.6	0.587
Univariate	(25, 27, 29, 31)	975	1.525 (1.244–1.871)	<0.001	1.525 (1.244–1.871)	<0.001	0.472	0	

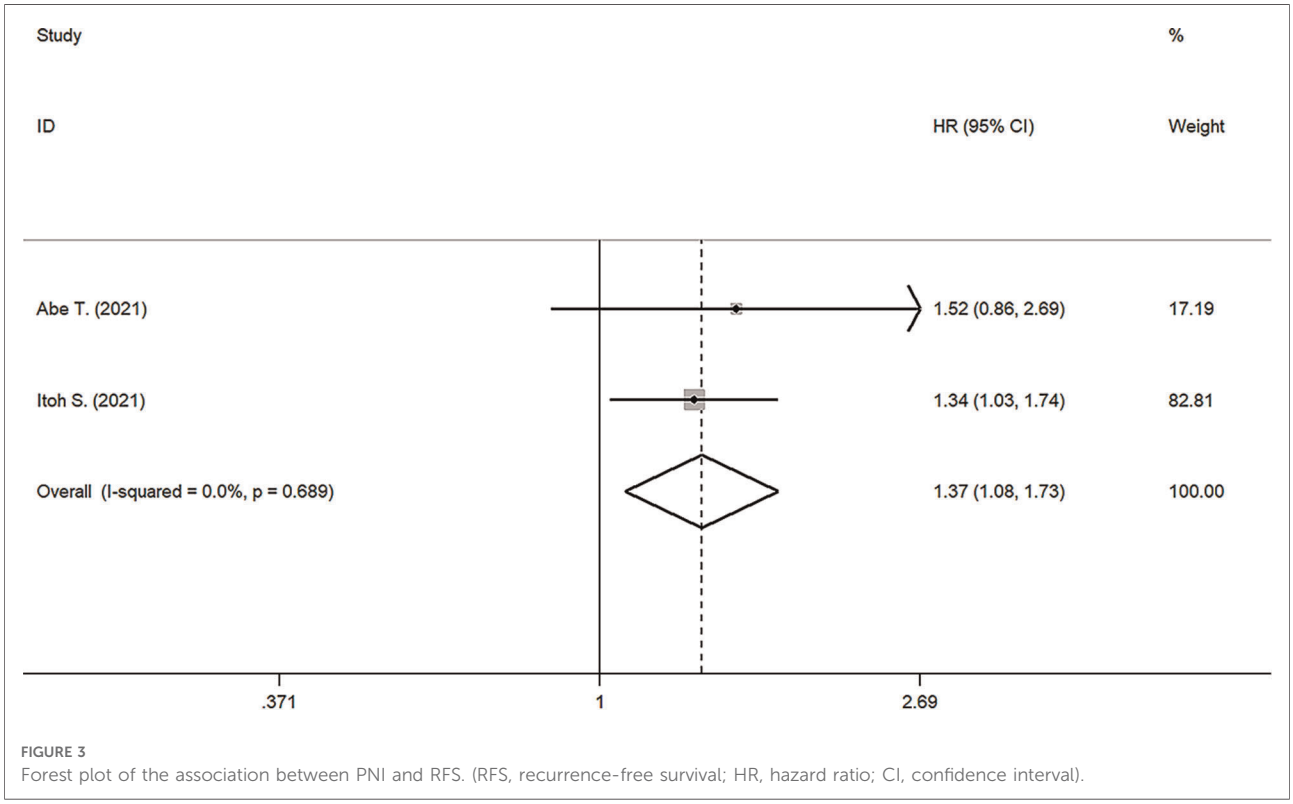

FIGURE 3
Forest plot of the association between PNI and RFS. (RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval).

significant effect on the pooled HR (Figure 4). Furthermore, publication bias was investigated, and there was no obvious asymmetry in the funnel plot upon visual inspection (Figure 5), then Begg's and Egger's tests yielded *p* values of 0.228 and 0.702, respectively, which indicated that there was no distinct publication bias among included studies.

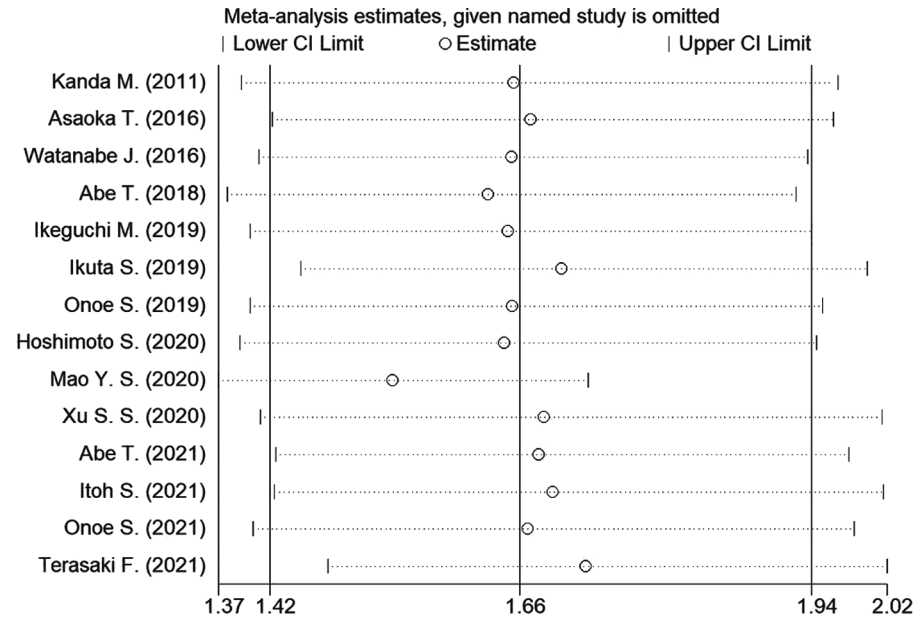

FIGURE 4
Sensitivity analysis of the relationship between PNI and OS. (OS, overall survival).

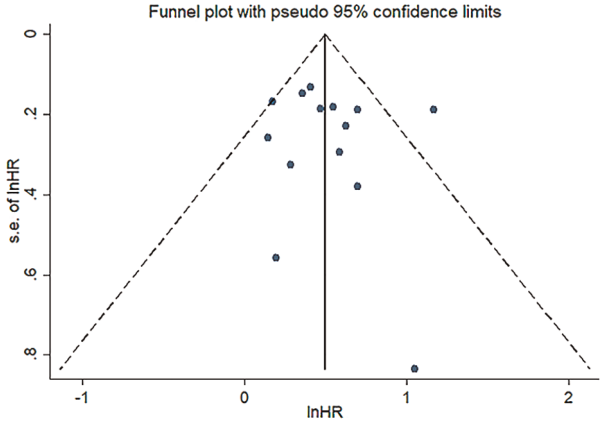

FIGURE 5
Funnel plot illustrating publication bias test result.

Discussion

Prognostic nutritional index (PNI) was previously known as a nutritional evaluation index, it has recently been reported to be useful to estimate postoperative morbidity and predict the prognosis in PDAC patients. In our meta-analysis, fourteen studies with a total of 3,385 patients were included (17–19, 22–32). The pooled results showed that lower preoperative PNI was association with poorer OS and RFS. Moreover, results from subgroup analyses and sensitivity analysis further validated the robustness of pooled results.

According to the meta-regression analysis, the diversity of cutoff value might be the source of heterogeneity. There were several methods to determine cutoff value. Among these studies, five studies were defined with a receiver operating characteristic curve (ROC) (17, 24, 27, 29, 31), three with the minimum *p* value approach (22, 25, 28), and one set the worst tertile of PNI as cutoff value (23). In other studies, mean or median value was used in two studies (30, 32), and three had no clear explanation (18, 19, 26). As a consequence, the cutoff value for PNI ranged from 36 to 53.10. The ROC curve approach maybe the most common way to identify cutoff value. The ROC could reflect the 1-specificity values (false positive rate, *X*-axis) and the sensitivity values (true positive rate, *Y*-axis) for each potential threshold, and we were able to determine the cutoff value with high accuracy. The minimum *p* value approach, also called maximal Chi square statistics approach, was another common method. Each value was assessed as potential threshold, and Chi squared tests were utilized. The maximal Chi square value corresponding threshold was recognized as the optimal cutoff value, however, the type I error rate might be higher due to multiple testing of this method (33, 34). The best way to determine cutoff value is still up for debate, and we have not been able to come to a consistent conclusion. Hence, more multi-institutional data analyses were required to reach a definitive conclusion about cutoff values.

PNI was calculated by albumin and lymphocyte. Albumin, mainly synthesized by hepatocytes, was closely related to nutritional status. Hypoalbuminemia showed the level of malnutrition and cachexia of cancers patients. Some cytokines

in tumor microenvironment, such as TNF-α, played an optimal role in the pathogenesis of malnutrition in pancreatic cancer (35). TNF-α could selectively inhibit the gene expression of albumin, causing hypoalbuminemia. Some research indicates that nutrition is a crucial determinant of immune response, which may be impaired by hypoalbuminemia (36). Thus, low levels of serum albumin can be recognized as a marker of poor prognosis in PDAC (37, 38). It was widely acknowledged that lymphocytes were indispensable components of immune system and tumor microenvironment (4). Immune surveillance was considered as the vital part of anti-tumor immunity, however, tumor cells might escape the surveillance by reducing CD4+ and CD8+ lymphocytes causing lymphocytopenia (39). Low lymphocyte counts lead to insufficient immunological responses in tumor microenvironment and result in cancer progression. In addition, the impairment of lymphocyte subsets may be reversed when resecting primary tumor (40). What is more, malnutrition and weak immune could increase the risk of postoperative complications, such as bleeding, pancreatic fistula and infection (26, 41). Therefore, PNI might be a promising predictor of prognosis in patients with PDAC.

There were several limitations in our meta-analysis. Firstly, all studies we selected are retrospective in design, so the potential bias was not inevitable. Secondly, the ethnicity of all included patients is Asian, and we expect the more similar studies can be conducted in Caucasians and Africans. Thirdly, HR and 95% CI of one study was estimated according to the survival curve (31), which might not be very accurate. It would affect the pooled HR. Fourthly, patients with tumor located in pancreas head usually underwent pancreaticoduodenectomy, while distal pancreatectomy or medial pancreatectomy were always performed when tumor locates in pancreas body or tail. Different surgical procedures were associated with different prognosis, and it may result in bias. Finally, all include studies were published in English, and potential publication bias cannot be ignored.

Conclusion

To sum up, our meta-analysis revealed that PDAC patients with lower preoperative PNI level had a worse prognosis. The limitation of this study also cannot be overlooked, and more well-designed studies with large sample size and different ethnicity are required to overcome these limitations.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Author contributions

PCZ, ZWW, CW and BLT conceived and designed the study. PCZ, ZWW, XH and ZHW were responsible for the collection and assembly of data, data analysis, and interpretation. PCZ, ZWW, and CW were involved in writing the manuscript. PCZ, XH, ZHW and BLT revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.992641/full#supplementary-material.

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Impact of age on short-term outcomes after pancreaticoduodenectomy: A retrospective case-control study of 260 patients

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Background: Although the increase of perioperative complications in the elderly undergoing pancreaticoduodenectomy (PD) surgery has been recognized, the definition of the "old patient" of PD in the studies is different and there is no accepted cut-off value at present.
Methods: 279 consecutive patients who have undergone PD in our center between January 2012 and May 2020 were analyzed. Demographic features, clinical-pathological data and short-term outcomes were collected. The patients were divided into two groups, and the cut-off value (62.5 years) is picked based on the highest Youden Index. Primary endpoints were perioperative morbidity and mortality, and complications were classified according to the Clavien-Dindo Score.
Results: A total of 260 patients with PD were included in this study. Postoperative pathology confirmed pancreatic tumors in 62 patients, bile duct tumor in 105, duodenal tumor in 90, and others in 3. Age (OR = 1.09, $P < 0.01$), and albumin (OR = 0.34, $P < 0.05$) were significantly correlated with postoperative Clavien-Dindo Score ≥3b. There were 173 (66.5%) patients in the younger group (<62.5 years) and 87 (33.5%) in the elderly group (≥62.5 years). Significant difference between two groups was demonstrated for Clavien-Dindo Score ≥3b ($P < 0.01$), postoperative pancreatic fistula ($P < 0.05$), and perioperative deceases ($P < 0.05$).
Conclusions: Age and albumin were significantly correlated with postoperative Clavien-Dindo Score ≥3b, and there was no significant difference in predicting the grade of Clavien-Dindo Score. The cut-off value of elderly patients with PD was 62.5 years old and there were useful in predicting Clavien-Dindo Score ≥3b, pancreatic fistula, and perioperative death.

KEYWORDS
pancreaticoduodenectomy, age groups, elderly patients, Clavien-Dindo score, POPF

1. Introduction

As important basic data in medicine, age is directly related to decision when surgeons consider the operation. A patient's age can affect the complication and prognosis after surgery, and the patient of elderly often suggests poor surgical outcomes (1, 2). In 2019, 617 million people are 65 years old or older; by 2050, the number will reach 1.6 billion—nearly 20% of the world's population (3). Inevitably, surgeons have to be confronted with the surgical choices of more elderly patients.

Pancreaticoduodenectomy (PD) is still burdened by high rates of complication and mortality (4). The poor outcomes of PD is primarily owing to the highly malignant periampullary neoplasms and the great trauma of operation on human body (5). Considering the potentially higher risks of age-related complication and mortality, the decision to submit elderly to PD would be challenging (6, 7). Early identification of elderly patients, combination of perioperative vigilance and proper treatment may help to reduce the incidence of serious complications and postoperative death. However, how to define the elderly in PD remains controversial. At present, the age group of patients with PD surgery is based on the aging population (8). The criteria for the elderly in some research were the aging criteria of the World Health Organization, such as 65 and 75 years old (9). In another study, regarding the age of 70 as the standard of the elderly is a subjective judgment (9, 10). There is a lack of calculation of the cut-off value of the age of patients with PD (11).

In the present study, we aimed to analyze the effect of age on short-term outcomes in patients undergoing PD and to determine the criteria for the elderly for PD. In particular, it was desired to determine whether differences exist between young and elderly people in postoperative complications and mortality. By calculating the cut-off value of age for PD, the short-term prognosis evaluation effect was calculated, which is helpful for the judgment of PD.

2. Methods

2.1. Patients

The medical records of all patients who underwent PD in our center between January 2012 and May 2020 were analyzed (n = 279). 19 subjects were excluded because of lack of data or other concomitant procedures (**Figure 1**). The same surgical team performed all PD using the same procedure, and pathological examination was performed after operation. Age, sex, body mass index (BMI), hypertension, diabetes, hemoglobin, total bilirubin, albumin, complication, re-operation, perioperative mortality (30-day or in-hospital), hospital stay, cost, readmission (90 days of initial discharge), and tumor pathological characteristics were recorded for each participant. The study was approved by the ethics committee of the General Hospital of Western Theater Command and was conducted in accordance with the principles of the Helsinki declaration. The ethical approval number is 2021EC2-26.

2.2. Surgical technique and postoperative management

The PD was performed by the fixed team, which was composed of five experienced pancreatic surgeons, including at least two attending surgeons. All patients were performed standard Whipple operation for side-to-side gastrojejunal anastomosis, end-to-side biliary jejunal anastomosis and end-to-side pancreatic jejunal anastomosis. The extraperitoneal drainage tube was placed behind the cholangiojejunostomy and pancreaticojejunostomy. Antibiotics were used prophylactically during operation and octreotide was used routinely after operation. The abdominal drainage tube was removed if the amylase level of drainage fluid was normal for three consecutive times after operation.

2.3. Classification of surgical complications

Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment orsurgical, endoscopic, and radiological interventions.

Grade Il: Requiring pharmacological treatment with drugs other than such allowed for grade I complicationsBlood transfusions and total parenteral nutrition are also included.

Grade Ill: Requiring surgical,endoscopic or radiological intervention.

Grade Illa: Intervention not under general anesthesia.

Grade Illb: Intervention under general anesthesia.

Grade IV: Life-threatening complication requiring IC/ICU management.

Grade IVa: Single organ dysfunction (including dialysis).

Grade IVb: Multiorgan dysfunction.

Grade V: Death of a patient.

2.4. Definition of complications

Postoperative complications were defined as follows, and Clavien-Dindo Score was used to evaluate the postoperative complications (12–15):

Biliary leak: bilious drainage from intraoperatively placed drains or radiographically proven fluid collection requiring percutaneous drainage and demonstrating elevated bilirubin levels.

Postoperative pancreatic fistula (POPF): POPF is now redefined as a drain output of any measurable volume of fluid with an amylase level >3 times the upper limit of institutional normal serum amylase activity three days later after surgery, associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula.

Chyle leak: Chyle leak was defined as output of milky-colored fluid from a drain, drain site, or wound on or after postoperative day 3, with a triglyceride content ≥110 mg/dl (≥1.2 mmol/L).

Postoperative bleeding: Blood loss proved by various ways, such as hematemesis, hematochezia or melena.

Intraperitoneal infection: Intraperitoneal fluid obtained from percutaneous drainage with culture-proven bacterial organisms.

Delayed gastric emptying: radiological evidence of delayed gastric emptying or post-operative nasogastric tube decompression longer than 2 weeks.

Pulmonary infection: fever, leukocytosis, sputum with leukocytosis, on culture of sputum demonstrating a pathogen, and chest radiograph demonstrating focal infiltrates.

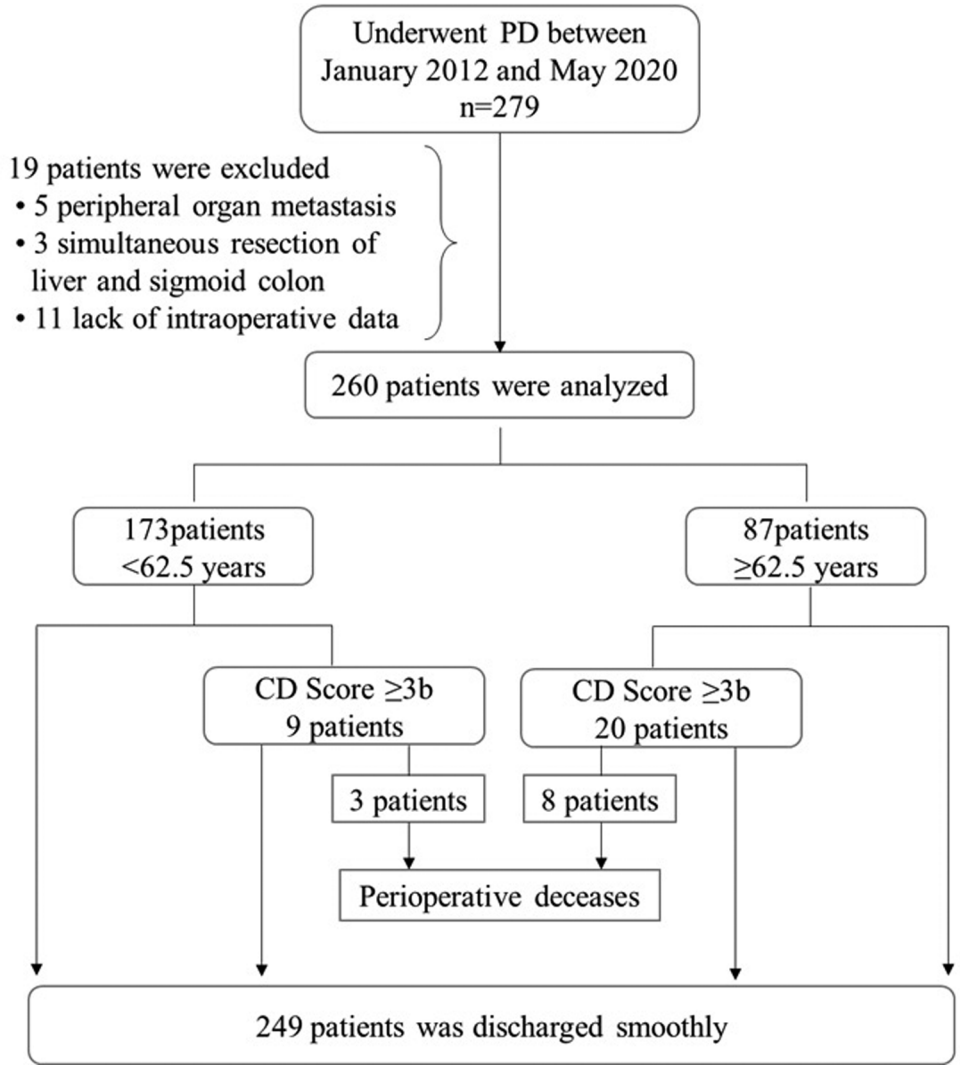

FIGURE 1
Inclusion, exclusion and outcomes of patients. CD Score, Clavien-Dindo Score; PD, Pancreaticoduodenectomy.

Incision dehiscence: any disruption of the skin closure with subcutaneous tissue exposure or a wound opening that required packing.

Pleural Effusion or Ascites: evidence of fluid collection on postoperative imaging.

Wound infection: Wound infection is defined as findings including purulent discharge, localized swelling, redness/heat, delayed wound healing, or positive wound culture results.

2.5. Statistical analysis

We report the categorical variables as absolute value and percentage value, continuous variables as average ± standard deviation, and asymmetrical distribution (Skewed distribution) continuous variables are presented as median [interquartile range]. A *P*-Value <0.05 was considered statistically significant. A univariate logistic regression analysis was then performed to identify preoperative variables associated specifically with perioperative complication (Clavien-Dindo Score ≥3b). Variables tested in this analysis included age, sex, BMI, comorbidities (hypertension, diabetes), and laboratory value (hemoglobin, total bilirubin, albumin). Multivariable analyses were carried out in variables with significant differences in univariate logistic analysis. The strength of the association between postoperative complications and age was evaluated by calculating the area under the respective receiver operating characteristic (ROC) curves. This is defined as $Y = \text{sensitivity} + \text{specificity} - 1$ and ranges from 0 to 1. The dimensional cut-off maximizing the balance between sensitivity and specificity in predicting greater postoperative complications was identified through calculation of the Youden Index, and a cut-off value is picked based on the highest Youden Index. According to the cut-off value, the age groups were divided, and the short-term outcomes which included complications, perioperative deceases, readmission, hospital stay (length of stay after operation), and cost were

analyzed. Comparison between the frequencies of the categorical variables (complications, perioperative deceases, readmission,) was assessed using the Chi-square test. The Mann-Whitney U test was used to compare the differences between hospital stay, cost, and in pairs of group. The variables which significant differences in univariate logistic with Clavien-Dindo score were analyzed by ordinal logistic analysis. Calculating the coefficient of regression, the OR value was calculated by SPSS data transformation. All statistical analyses were performed using SPSS version 25.0 software (SPSS Inc. Chicago, IL, United States).

3. Results

3.1. Patient characteristics

Patient characteristics: During the study period, 279 patients underwent PD with the same procedure by the same surgical team. The cases from 19 subjects were excluded from the analysis due to insufficient medical record, and the final index population was composed of 260 subjects. 62 PD were performed for pancreatic tumor, 109 patients underwent PD for bile duct tumor, 90 patients underwent PD for Duodenal tumor, and 3 patients underwent PD for others. The details of these patients are represented in Table 1. Among the continuous variables, only albumin was in normal distribution (average ± standard deviation), and the rest were expressed as median [interquartile range].

TABLE 1 Patient characteristics (n = 260).

Variable	*
Age (years, range 33–82)	59 [51–64]
Gender	
Female	107 (41.2)
Male	153 (58.8)
Height (cm)	160 [156–165]
Weight (kg)	57 [51–62]
BMI (kg/m^2)	22.2 [20.2–24.2]
Underweight (≤18.5)	22 (8.5)
Normal (18.5–25)	197 (75.8)
Overweight (25–30)	37 (14.2)
Obese (≥30)	4 (1.5)
Comorbidities	
Hypertension	45 (17.3)
Diabetes	30 (11.5)
Laboratory value	
Hemoglobin (g/dl)	12.7 [11.3–13.88]
Total bilirubin (μmol/L)	140.7 [29.2–229.3]
Albumin (g/dl)	4.1 ± 0.4
Diagnoses	
Pancreatic tumor	62 (23.8)
Bile duct tumor	105 (40.4)
Duodenal tumor	90 (34.6)
Others	3(1.2)

*Data are shown as mean ± SD, median [interquartile range] or absolute n (%). BMI, body mass index.

3.2. Univariate and multivariate logistic analyses

The age, sex, BMI, comorbidities (hypertension, diabetes), and laboratory value (hemoglobin, total bilirubin and albumin) were used to evaluate the occurrence of Clavien-Dindo Score ≥3b after operation in univariate logistic regression analysis. Age (OR = 1.09, P = 0.002), hemoglobin (OR = 0.86, P = 0.056) and albumin (OR = 0.34, P = 0.014) were significantly correlated with postoperative complications. Multivariable analyses were carried out in age, hemoglobin, albumin, and patients who evaluated Clavien-Dindo Score ≥3b. Only Age (OR = 1.08, P = 0.01) was significantly correlated with postoperative complications (Table 2).

3.3. ROC curve analysis

At ROC curve analysis, age correlated with prediction of Clavien-Dindo Score ≥3b (AUC of 0.71, 95%CI 0.62–0.81, P < 0.001).Point-by point analysis of the ROC curve identified 62.5 years as the cut-off value maximizing the balance of sensitivity and specificity in the prediction of Clavien-Dindo Score ≥3b (Figure 2). According to the cut-off point of 62.5 years old, patients were divided into two groups: group I (<62.5 years) and group II (≥62.5 years). The short-term outcomes (complications, reoperation perioperative deceases, readmission, hospital stay, and cost) were analyzed in Table 3.

3.4. Short-term outcomes of two groups

There were 173 (66.5%) patients in group I and 87 (33.5%) in group II. Complications are reported in Table 3: no significant differences were reported for biliary leak, postoperative bleeding, intraperitoneal infection, delayed gastric emptying, pulmonary infection, incision dehiscence, pleural effusion, ascites, wound infection, reoperation, readmission hospital stay, and cost. Perioperative deceases were 11 (4.2%), including 8 (9.2%) from

TABLE 2 Univariate and multivariate analyses of preoperative predictors associated with the occurrence of Clavien-Dindo Score ≥3b.

Pre-operative variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (years)	1.09	1.04–1.15	**<0.001**	1.08	1.03–1.14	**0.001**
Male	0.73	0.32–1.63	0.440			
BMI (kg/m^2)	1.01	0.89–1.12	0.863			
Comorbidities						
Hypertension	0.50	0.21–1.21	0.126			
Diabetes	1.15	0.32–4.04	0.831			
Laboratory value						
Hemoglobin (g/dl)	0.86	0.74–1.00	**0.056**	0.90	0.75–1.08	0.239
Total bilirubin(μmol/L)	1.00	1	0.930			
Albumin (g/dl)	0.34	0.14–0.80	**0.014**	0.54	0.20–1.44	0.218

BMI, body mass index.
Bold values indicates the P value of potential key indicators.

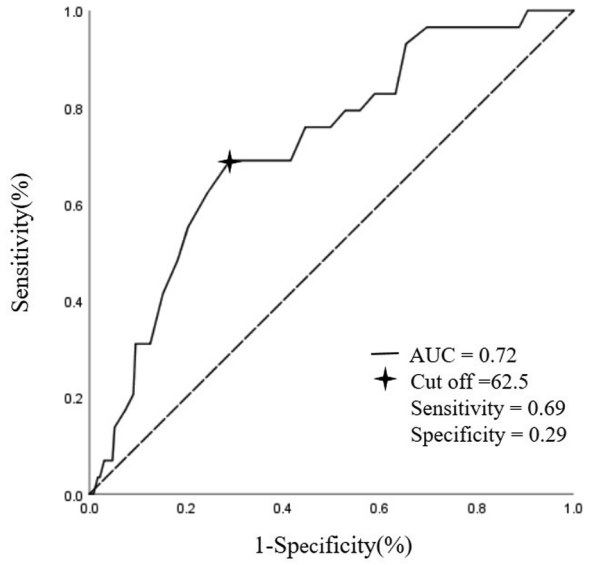

FIGURE 2
Age correlated with prediction of clavien-dindo score ≥3b in ROC curve analysis. AUC, area under curve.

TABLE 3 Short-term outcomes of two groups who had undergone pancreaticoduodenectomy.

Pre-operative variable	Group I (173 pts < 62.5 yrs)	Group II (87 pts ≥ 62.5 yrs)	*P*-value
Clavien-Dindo Score ≥3b, *n* (%)	9 (5.2)	20 (23.0)	**<0.001**
Biliary leak, *n* (%)	5 (2.9)	2 (2.3)	1
POPF, *n* (%)	12 (6.9)	13 (14.9)	**0.039**
Chyle leak, *n* (%)	7 (4.0)	3 (3.4)	1
Postoperative bleeding, *n* (%)	15 (8.7)	7 (8.0)	0.864
Intraperitoneal infection, *n* (%)	20 (11.6)	11 (12.6)	0.799
Delayed gastric emptying, *n* (%)	11 (6.4)	10 (11.5)	0.152
Pulmonary infection, *n* (%)	17 (9.8)	7 (8.0)	0.640
Incision dehiscence, *n* (%)	0	0	1
Pleural effusion, *n* (%)	45 (26.0)	25 (28.7)	0.640
Ascites, *n* (%)	56 (32.4)	26 (29.9)	0.684
Wound infection, *n* (%)	20 (11.6)	5 (5.7)	0.134
Reoperation, *n* (%)	5 (2.9)	2 (2.3)	0.781
Perioperative deceases, *n* (%)	3 (1.7)	8 (9.2)	**0.013**
Readmission, *n* (%)	29 (16.8)	10 (25.6)	0.262
Hospital stay (days)	15 [12–21]	16 [13–22]	0.332
Cost (¥)	77,753.2 [58,554.4–94,430.9]	82,518.5 [60,284.8–105,890.3]	0.162

Data are shown as median [interquartile range] or absolute *n* (%).
Perioperative deceases: death within 30 days of surgery or during the index hospitalization. POPF, Postoperative pancreatic fistula; Hospital stay, length of stay after operation.
Bold values indicates the P value of potential key indicators.

among the group II ($P = 0.013$). Rates of complications with grade ≥3b, according to the Clavien-Dindo Score, were significantly different between the two groups, as well as incidence of POPF (6.9% in group I vs. 14.9% in group II; $P = 0.039$).

3.5. Ordinal logistic analysis

The age, hemoglobin and albumin that had influence on Clavien-Dindo ≥3b status were included in the preoperative variables, and then the ordinal logistic analysis was used to analyze the influence on the grade of Clavien-Dindo Score (Table 4). It can be seen that age (OR = 1.02, $P = 0.085$), hemoglobin (OR = 1.00, $P = 0.936$) and albumin (OR = 1.32, $P = 0.378$) have no significant effect on the level of Clavien-Dindo Score.

4. Discussion

The world's population is aging rapidly. In parallel, the rate of neoplastic diseases and the number of surgical operations is rising steeply. Despite the poor outcomes, PD is the best choice for the treatment of periampullary neoplasms. The high risk of outcomes are mainly owing to the high postoperative morbidity and mortality rates. Consequently, careful selection before surgery is the key to excellent outcomes. The top factor which attracts the attention of surgeons was age, and the advanced age of patients tends to be closely related to higher postoperative complications. However, the definition of the "old patient" in terms of age varies across the studies is not worldwide accepted and different age cut-off, such as 65, 70, 75, and 80 years have been used in the studies of PD (3, 16).There is a lack of age grouping based on postoperative complications of PD. As an operation with huge trauma, defining the cut-off of elderly patients in PD can be conducive to predicting poor prognosis.

In the present study, we calculated the influence of preoperative and pathological data of 260 PD patients on Clavien-Dindo ≥3b status. In univariate logistic regression analysis, age, hemoglobin and albumin had significant effect on Clavien-Dindo ≥3b status. Age (OR = 1.09, $P = 0.002$) is a risk factor for postoperative complications, while hemoglobin (OR = 0.86, $P = 0.056$) and albumin (OR = 0.34, $P = 0.014$) are protective factors. Nutritional status before surgery is regarded as one of the key factors that influence outcomes after operation, several studies on PD have indicated the importance of maintaining normal preoperative albumin levels (17, 18). Subsequent multivariate logistic regression analysis showed that age was significantly correlated with prognosis (OR = 1.08, $P = 0.01$). Consistent with other studies, old age is an independent risk factor for complications after PD, but there is no clear cut-off point for the division of age. At ROC curve analysis, age correlated with Clavien-Dindo ≥3b status (AUC = 0.72, cut-off = 62.5). Sensitivity, and

TABLE 4 Ordinal logistic analysis of predictors of Clavien-Dindo score in patients who underwent PD.

Variable	OR	95% CI	*P*-value
Age (years)	1.02	1.00–1.05	0.085
Hemoglobin (g/dl)	1.00	0.90–1.13	0.936
Albumin (g/dl)	1.32	0.71–2.44	0.378

specificity of possible cut-offs for age are displayed in Figure 2. This is different from the cut-off value of aging in developed countries (65 years), which may be due to the consumption of body by malignant tumor and the larger injury of PD (19–21).

Although elderly patients were not the absolute contraindication of PD, the incidence rate of postoperative complications was higher in elderly patients. In our research, the patients were divided into two groups according to 62.5 years old: group I (<62.5 years) and group II (≥62.5 years). The short-term outcomes (complications, perioperative deceases, readmission, hospital stay, and cost) were analyzed. Among the complications, only Clavien-Dindo >3b status (5.2% in group I vs. 23.0% in group II; $P < 0.001$) and POPF (6.9% in group I vs. 14.9% in group II; $P = 0.039$) had significant differences between the two groups, and the incidence rate of the second group was significantly higher than that of the first group. The Clavien-Dindo grade and POPF showed the same trend because the main complication requiring intervention after PD was pancreatic fistula and the pancreatic anastomosis carries the highest risk of leak and cause of morbidity and mortality (22, 23). Elderly patients were prone to POPF for the following reasons: firstly, elderly patients were complicated with more basic diseases, and anastomotic edema was vulnerable to cause POPF; Second, postoperative infection increased the incidence of pancreatic fistula because of poor immunity; Third, weak physical conditions were often not conducive to the recovery of anastomotic stoma, resulting in anastomotic failure. Due to the high incidence rate of POPF and the weakness of the elderly, the perioperative mortality of the group I was significantly higher than the group II (1.7% in group I vs. 9.2% in group II; $P = 0.013$).

In terms of postoperative management, there were no significant difference in reoperation readmission, hospital stay and cost. The ordinal logistic analysis was used to analyze age (OR = 1.02, $P = 0.085$), hemoglobin (OR = 1.00, $P = 0.936$) and albumin (OR = 1.32, $P = 0.378$) on the grade of Clavien-Dindo Score, while all of them had no significant effect on this grade. We speculate that the number of high-grade of Clavien-Dindo Score is less leading to unclear judgment.

With the development of surgical technology and neoadjuvant therapy, the elderly have no longer been the forbidden area of PD surgery (7, 24, 25). However, compared with the young, the postoperative complications and mortality of the elderly have significantly increased (26, 27). Elderly patients were more likely to develop POPF and Clavien-Dindo Score ≥3b than younger ones, probably as a result of the poor recovery of pancreaticojejunostomy, frailty, and the decrease of physical tolerance in the elderly (28–30). Our research further supports the above view.

The difference is that the age group used in our study is not the commonly used 65 year old age limit in developed countries, or 75 and 80 years old in other PD prognosis studies, but the best cut-off value of 62.5 years old selected after calculating the dimensional cut-off maximizing the balance between sensitivity and specificity by analyzing the characteristics of PD patients in our hospital. Surgeons can refer to this cut-off value before making surgical decisions, and be vigilant for elderly patients to reduce postoperative complications.

The main limitation of this study is the retrospective nature and the resulting selection bias, because the cases extracted from our center were used to represent the analyzed population. Additionally, due to the difficulty of long-term follow-up, we cannot collect the long-term outcomes after PD. Therefore, further multicenter prospective studies or basic research will be needed to understand the influence of age on the short-term and long-term outcomes of PD patients.

In conclusions, age, hemoglobin and albumin were significantly correlated with postoperative Clavien-Dindo Score ≥3b in preoperative variables. According to 260 cases in our center, the cut-off value of elderly patients with PD was 62.5 years old and there were significant differences in postoperative Clavien-Dindo Score ≥3b, pancreatic fistula, and perioperative death between the elderly and young group. However, age, hemoglobin and albumin were no significant differences in predicting the grade of Clavien-Dindo Score.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of General Hospital of Western Theater Command. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZZ: Conceptualization; data curation; formal analysis; writing–original draft; writing—review and editing. ZS: Data curation; formal analysis; investigation; project administration; writing—review and editing. TY: Data curation; writing—review and editing; formal analysis. ZL: software; writing—original draft; writing—review and editing. JH: Conceptualization; formal analysis; methodology; writing—review and editing. TZ: Conceptualization; formal analysis; methodology; writing—review and editing. DR: project administration; resources; writing—original draft; writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

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