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Influence of non-jaundice stage at diagnosis on clinicopathological features and long-term survival of patients with periampullary carcinomas

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Abstract

The effect of non-jaundice stage at diagnosis on clinicopathological features and prognosis of patients with periampullary carcinomas (PACs) remains uncertain.

The 504 patients who were pathologically diagnosed with PACs between 2012 and 2017 were retrospective analyzed. Kaplan–Meier method was used to estimate survival and log-rank tests were used for comparisons between groups.

Patients were divided into the non-jaundice group and the jaundice group according to serum total bilirubin (3 mg/dL) at diagnosis. By comparison with the jaundice group, more patients of the non-jaundice group manifested abdominal pain with longer duration. The degree of deterioration of complete blood count, liver function and CA19-9 in the non-jaundice group was significantly lower ($P < .001$). The non-jaundice group had larger tumor size ($P = .001$), more duodenal carcinoma and pancreatic carcinoma ($P < .001$), lower resection rate ($P = .001$) and less pancreatic and perineural invasion ($P = .017$, $P = .002$). The I stage was significantly more common in the non-jaundice group ($P < .001$). The cumulative 5-year survival of the non-jaundice group was significantly higher ($P = .032$). Multivariate analysis for all patients demonstrated that CEA level, cell differentiation, chemotherapy, and recurrence were independent prognostic factors.

Patients with PACs in a non-jaundice stage at diagnosis showed more favorable clinicopathological features and long-term survival than such patients with jaundice.

Abbreviations: AC = ampullary carcinoma, CT = computed tomography, DC = duodenal carcinoma, DCC = distal cholangiocarcinoma, ERCP = endoscopic retrograde cholangiopancreatography, MRCP = magnetic resonance cholangiopancreatography, MRI = magnetic resonance imaging, PACs = periampullary carcinomas, PC = pancreatic carcinoma, PD = pancreatoduodenectomy, US = transabdominal ultrasound.

Keywords: clinicopathological features, long-term survival, non-jaundice stage, periampullary carcinomas

1. Introduction

Periampullary carcinomas (PACs) originate within 2 cm of radius of the major papilla in the duodenum. They are comprised of 4 subgroups: duodenal carcinoma (DC), distal cholangiocarcinoma (DCC), ampullary carcinoma (AC) and, pancreatic carcinoma (PC).[1] PACs account for 5% of all gastrointestinal tract malignancies.[2] In recent years, the incidence of PACs shows a tendency to ascend. Pancreatoduodenectomy (PD) with or without pylorus preservation is considered to be the optimal treatment for these malignant tumors.[3] The 5-year survival of PACs after resection has been reported between 15% and 65%.[4] The poor prognosis is due to few specific symptoms in primary stages of PACs.[5] Although the origins are different, these tumors usually have similar manifestations because of the complex regional anatomy and close locations. Among of these, jaundice is one of the most common clinical symptoms.[2,6] About 70% to 80% patients with PACs will present obstructive jaundice during the natural progression of the disease.[6,7] However, there are a few patients did not manifest jaundice at diagnosis.[8–11] Although several studies have reported factors affecting long-term survival beyond 5 years in patients subjected to resection,[1,3,12–17] the effect of jaundice on the prognosis of PACs patients is still uncertain. The main aim of the present study was

Editor: Neil Merrett.

This work was supported by National Natural Science Foundation of China 81001103, 81472325, and 81870457.

The authors report no conflicts of interest.

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How to cite this article: Peng X, Jiao X, Zhao P, Zhu R, Sun Y, Zhou L. Influence of non-jaundice stage at diagnosis on clinicopathological features and long-term survival of patients with periampullary carcinomas. Medicine 2019;98:45(e17673).

Received: 24 April 2019 / Received in final form: 24 September 2019 / Accepted: 29 September 2019

http://dx.doi.org/10.1097/MD.0000000000017673

to compare the differences of clinical, laboratorial, radiological, pathological, and treatment characteristics between patients of PACs with and without jaundice at diagnosis and confirm the relationship between jaundice and long-term survival in patients with PACs. The secondary objective was to identify the prognostic factors of patients with PACs.

2. Materials and methods

2.1. Patient identification and data collection

A retrospective analysis of patients who were pathologically diagnosed with PACs in our institution between January 2012 and December 2017. Institutional review board approval was obtained for this study. Tumors arising from the proximal-mid-duodenum, distal common bile duct, the ampulla of Vater and the head of pancreas were included in the study. Date for patients with other tumors, such as solid pseudopapillary neoplasms, gastrointestinal stromal tumors, neuroendocrine neoplasms, low- or high-grade intraepithelial neoplasia of adenomas, were excluded from the analysis. Data retrieved for analysis included demographic data, clinical data, imaging date, pathological data, types of treatment, postoperative complications, adjuvant treatment, and follow-up data.

2.2. Data analysis

2.2.1. Clinical features and perioperative assessment. Patient demographics included age, gender, and co-morbid illnesses. Clinical data included the duration of symptoms, clinical manifestations and preoperative laboratory results. The cut-off values for laboratory tests were chosen prior to analysis and were not altered according to the results. Jaundice was defined as a serum total bilirubin level ≥3 mg/dL, because patients usually presented yellowish skin or conjunctival membranes of the sclerae above this value.[6,8,18] Patients in the present study were divided into 2 groups according to serum total bilirubin at diagnosis: <3 mg/dL for non-jaundice group and ≥3 mg/dL for jaundice group. Primary diagnosis and preoperative staging of PACs was based on imaging examinations, including trans-abdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP).

2.2.2. Surgical procedures and adjuvant treatment. The 332 patients were treated by PD with or without pylorus-preserving. Thirty-nine patients were performed palliative by-pass surgery. Twenty patients were performed local resection. Adjuvant treatment was initiated for resected patients within 6 weeks following operation or those advanced patients who could not undergo surgery.

2.2.3. Postoperative assessment. Postoperative mortality was defined as death after the operation within 30 days. Postoperative complications included celiac or surgical site infection or bleeding, pancreatic leakage, bile leakage, delayed gastric function, etc. Recurrence included local and distant recurrence. A new hypodense mass or abnormal lymphadenopathy developed in the resected pancreas or mesenteric root region was considered evidence of local recurrence. Radiographic evidence of hypodense masses in the liver, lung or peritoneal seeding was considered to indicate distant recurrence.[19]

2.2.4. Histopathological evaluation. Pathological examination regarding the resected specimens, including tumor size and cell differentiation, primary sites, T stage, lymph node status, metastasis, resection margin status, pancreas infiltration, perineural, and intravascular invasion, were collected. Tumor size was defined as the maximum diameter of tumor at pathological examination. Tumor differentiation was graded as good, moderate or poor, with the worse grade for mixed differentiation. The origins of tumor were determined on gross and microscopic examination of the specimens. TNM staging was performed according to the 8th edition of the American Joint Committee on Cancer Staging Manual.

2.3. Statistical analysis

All continuous data were presented as the mean ± standard deviation, median and/or range. Categorical variables were expressed as numbers and percentages of the group from which they were derived. Continuous variables were compared using the Student t test for normally distributed data and Mann–Whitney U test for non-parametric data. The χ^2 test was used for categorical variables. Survival was estimated using the Kaplan–Meier method. Univariate analysis of various prognostic factors influencing the overall survival was performed using log-rank test. Factors with a significant association <0.1 in the univariate analysis were included in the multivariate analysis, which was performed using the Cox proportional hazard model. Statistical significance was considered when P value was <.05. The SPSS 21.0. software was used for statistical analysis.

3. Results

3.1. Patient demography and clinical characteristics

During the study period, 504 patients were pathologically diagnosed with PACs. Of those patients, 175 were non-jaundiced patients (serum total bilirubin <3 mg/dL) and 329 were jaundiced patients (serum total bilirubin ≥3 mg/dL). The mean age of entire cohort was 59.0 ± 11.0 years (range 21–89 years). The 304 (60.3%) patients were men. Median duration of symptoms was 4 weeks. Overall, apart from jaundice, weight loss was more common in the jaundice group. Besides, liver function was significantly worse in the jaundice group ($P < 0.001$). Nonspecific abdominal pain was the most common clinical presentation in the non-jaundice group, followed by dyspepsia symptoms like nausea, vomiting and anorexia. Moreover, Non-jaundiced patients significantly showed longer duration of symptoms and lower level of CA19-9 ($P < .001$). Patient demographic and clinical characteristics are described in Table 1.

3.2. Imaging features

The 442 of 504 patients underwent US and CT, 90.0%, 86.0% showed biliary dilatation and 50.2%, 78.3% detected neoplastic space-occupying lesions, respectively. The 241 of the cohort patients underwent MRI/MRCP, 93.8% discovered dilated bile ducts and 73.0% detected neoplastic masses. The 113 (97.4%) of 116 patients who underwent ERCP detected tumor masses. Biliary dilatation was more common in jaundiced patients than in the non-jaundice group who underwent examinations of US and CT ($P < .001$). The sensitive of biliary dilatation detecting by MRI/MRCP was equivalent in both groups ($P = .179$). There was no significant difference between the patients with and without

Table 1

Comparison of demographic data and characteristics for all patients with periampullary carcinomas between 2 groups (n = 504).

Characteristics	Serum total bilirubin at diagnosis (mg/dL)		*P* value
	<3 (non-jaundice group)	≥3 (jaundice group)	
Number of patients	175	329	
Age (years)	59.2 ± 11.5 (21–88)	58.9 ± 10.7 (26–89)	.760
Male: Female	96: 79	208: 121	.068
Cardiovascular disease, n (%)	44 (25.1%)	70 (70%)	.323
Nicotine consumption, n (%)	29 (16.6%)	42 (12.8%)	.242
Regular alcohol consumption, n (%)	6 (3.4%)	22 (6.7%)	.128
Family history, n (%)	25 (14.3%)	19 (5.8%)	.001
Duration of symptoms (weeks)	8 (0–336)	3 (0–96)	<.001
Symptoms, n (%)			
Jaundice	0 (0%)	262 (79.6%)	<.001
Abdominal pain	91 (55.5%)	119 (36.3%)	<.001
Body weight loss	24 (14.5%)	74 (22.6%)	.035
Fever	17 (10.3%)	13 (4.0%)	.005
Anemia, n (%)	111 (63.4%)	216 (65.7%)	.618
Total bilirubin (mg/dL)	0.9 (0.2–2.9)	10.2 (3.0–33.2)	<.001
ALT (IU/L)	95.5 (8.0–601.0)	182.0 (6.0–1397.0)	<.001
AST (IU/L)	67.0 (12.0–452.0)	121.0 (23.0–1113.0)	<.001
γ-GT (IU/L)	577.5 (12.0–2309.0)	810.0 (44.0–2874.0)	<.001
ALP (IU/L)	293.0 (46.0–1300.0)	520.0 (108.0–2001.0)	<.001
Albumin (g/L)	38.6 (27.1–50.2)	36.7 (19.8–48.6)	<.001
Pre-albumin (g/L)	173 (44.0–457.0)	139 (23.0–347.0)	<.001
CA19–9≥37U/mL, n (%)	80 (50.6%)	243 (81.3%)	<.001
CEA≥5ng/mL, n (%)	22 (14.3%)	64 (21.8%)	.056
Surgery, n (%)			.001
PD	105 (60.0%)	227 (69.0%)	
Palliative by-pass surgery	9 (5.1%)	30 (9.1%)	
Local resection	4 (2.3%)	15 (4.6%)	
None of operations	57 (32.6%)	57 (17.3%)	
Diagnosis of primary tumor, n (%)			<.001
DC	104 (59.4%)	138 (41.9%)	
DCC	31 (17.7%)	142 (43.2%)	
AC	12 (6.9%)	21 (6.4%)	
PC	28 (16.0%)	28 (8.5%)	
Chemotherapy, n (%)	72 (41.1%)	136 (41.3%)	.966
Radiotherapy, n (%)	8 (4.6%)	14 (4.3%)	.869
Recurrence, n (%)	29 (16.6%)	61 (18.5%)	.583

Data are presented as mean± standard deviation (range), median (range) or n (%).

γ-GT = γ-glutamyl transpeptidase, AC = ampullary carcinoma, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, DC = duodenal carcinoma, DCC = distal cholangiocarcinoma, PC = pancreatic carcinoma, PD = pancreaticoduodenectomy.

jaundice in the detection of neoplastic masses by CT, MRI/MRCP and ERCP ($P = .270$, $P = 385$, $P = 162$).

3.3. Treatment

In the study period, PD operation was performed in 332 of all patients (65.9%). The tumor resection rate of PD in the non-jaundice group (60.0%) was lower than that in the jaundice group (69.0%) ($P = .043$). In the rest of 172 patients, there was no statistically significant difference between the 2 groups who were performed local resection and palliative by-pass surgery. The overall incidences of postoperative complications and postoperative mortality of PD were 20.5% and 4.8%, respectively. The results showed that there was no significant difference between the 2 groups on both counts ($P = .189$, $P = .974$). The 208 patients received adjuvant therapy, 147 of them underwent postoperative chemotherapy and the difference was not statistically significant in the rate of chemotherapy between groups ($P = .286$). The patient treatment details are depicted in Table 2.

3.4. Pathological analysis

It is notable and distinguishable from the previous studies that the most common subgroup in the present study was DC (48.0%), followed by DCC (34.3%), PC (11.1%), and AC (6.5%). The non-jaundice group had more DC and PC while the jaundice group had more DCC ($P < .001$). According to 332 resected periampullary tumor specimens, the overall median tumor size was 2 cm (range 0.5–12 cm). The median tumor size of non-jaundiced patients was larger than that in the jaundice group ($P = .001$). In comparison with the jaundice group, tumors of stage I were significantly more common and the incidences of pancreatic and perineural invasion were significantly lower in patients of the non-jaundice group ($P < .001$, $P = .017$, $P = .002$). The pathological details of the study groups are detailed in Table 2.

3.5. Oncological outcomes

On multivariate analysis of patients with PACs who underwent PD showed that poor cell differentiation, absence of postoperative chemotherapy and presence of postoperative recurrence

Table 2

Comparison of pathological outcomes for patients with periampullary carcinomas submitted to pancreatoduodenectomy between 2 groups (n = 332).

Characteristics	Serum total bilirubin at diagnosis (mg/dL)		*P* value
	<3 (non-jaundice group)	≥3 (jaundice group)	
Number of patients	105	227	
Tumor size (cm)	2.5 (0.5–12)	2.0 (0.5–7)	.001
Stage, n (%)			<.001
I	50 (47.6%)	59 (26.0%)	
II	34 (32.4%)	136 (59.9%)	
III	15 (14.3%)	25 (11.0%)	
IV	6 (5.7%)	7 (3.1%)	
T-factor, n (%)			.054
T1+T2	66 (62.9%)	117 (51.5%)	
T3+T4	39 (37.1%)	110 (48.5%)	
N-factor, n (%)			.369
N0	88 (83.8%)	180 (79.6%)	
N1+N2	17 (16.2%)	46 (20.4%)	
M-factor, n (%)			.183
M0	105 (100%)	221 (97.8%)	
M1	0 (0%)	5 (2.2%)	
Cell differentiation, n (%)			.187
Good	3 (3.3%)	5 (2.4%)	
Moderate	69 (75.8%)	139 (66.5%)	
Poor	19 (20.9%)	65 (31.1%)	
Pancreatic invasion, n (%)			.017
Negative	83 (79.8%)	150 (67.0%)	
Positive	21 (20.2%)	74 (33.0%)	
Perineural invasion, n (%)			.002
Negative	93 (88.6%)	166 (73.8%)	
Positive	12 (11.4%)	59 (26.2%)	
Venous invasion, n (%)			.319
Negative	99 (94.3%)	205 (91.1%)	
Positive	6 (5.7%)	20 (8.9%)	
Resection margins, n (%)			.577
R0	103 (99.0%)	222 (98.2%)	
R1	1 (1.0%)	4 (1.8%)	
Postoperative complications, n (%)			.189
No	79 (75.2%)	185 (81.5%)	
Yes	26 (24.8%)	42 (18.5%)	
postoperative mortality, n (%)			.974
No	100 (95.2%)	216 (95.2%)	
Yes	5 (4.8%)	11 (4.8%)	
Postoperative chemotherapy, n (%)			.286
No	63 (60.0%)	122 (53.7%)	
Yes	42 (40.0%)	105 (46.3%)	
Postoperative recurrence, n (%)			.242
No	91 (86.7%)	185 (81.5%)	
Yes	14 (13.3%)	42 (18.5%)	

Data are presented as median (range) or n (%).

Table 3

Univariate and multivariate survival of patients with periampullary carcinomas who underwent pancreaticoduodenectomy (n = 332).

Variable	Comparison	Univariate	Multivariate		
		P value	*P* value	HR	95% confidence interval
Age	<65 years vs ≥65 years	.096			
CA19-9	<37 U/mL vs ≥37U/mL	.003			
N-factor	No vs Yes	.068			
Cell differentiation	Good, Moderate vs Poor	.002	<.001	2.343	1.499–3.662
Postoperative chemotherapy	Yes vs No	<.001	<.001	2.722	1.728–4.286
Postoperative recurrence	No vs Yes	.099	<.001	2.515	1.569–4.029

Only those variables with a significant association <0.1 in the univariate model were candidates for the multivariate model.

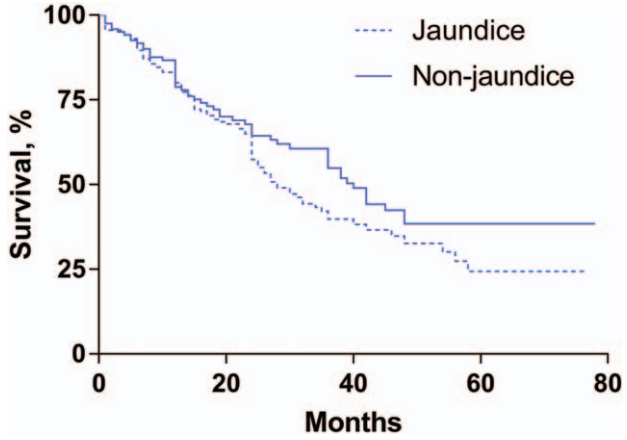

Figure 1. Kaplan–Meier curves showing survival of periampullary carcinomas with and without jaundice at diagnosis.

predicted poor outcomes. The univariate and multivariate analysis outcomes of resected patients by PD are depicted in Table 3.

In our cohort, the cumulative 5-year survival in the non-jaundice group (38.4%) was significantly higher than that in the jaundice group (24.3%) though there was no significant difference in the survival curves between the 2 groups ($\chi^2 = 4.582$, $P = .032$, Fig. 1). Multivariate survival analysis indicated that the factors of higher CEA level, poor cell differentiation, absence of chemotherapy and presence of recurrence had independent unfavorable prognostic impacts on survival (Table 4, Fig. 2).

3.6. Follow-up and survival

The 323 of 504 patients were followed up. Among of them, 248 patients were performed PD. The median duration of follow-up of all patients in this study was 19 months (range 1–78 months). The median and cumulative 5-year overall survival for the entire cohort were 35.0 months and 30.2%, respectively. Recurrence was seen in 90 patients of which 8 had only locoregional recurrence. The liver (60.0%) was the most common site of distant recurrence followed by lymph nodes (21.1%) and the lung (12.2%).

4. Discussion

This study examined the difference of clinicopathological features between patients of PACs with and without jaundice at diagnosis and the relationship between jaundice and cumulative 5-year survival in patients with PACs. Several previous literatures confirmed that the clinical course and outcomes of PACs at a non-jaundice stage were better than those in patients with jaundice at diagnosis.[7–10,18] In the present study, the presence or absence of jaundice at diagnosis was not showed as a prognostic factor by univariate and multivariate analysis, but the cumulative 5-year survival of 175 patients in the non-jaundice group was significantly higher than that of 329 patients in the jaundice group.

The onset of PACs without jaundice was insidious, and the main clinical manifestations were abdominal pain, fullness, fever, weight loss, nausea, and other non-specific symptoms,[6,9,10] which lasting for a longer time before consulting than patients who presenting jaundice at diagnosis. In this study, abdominal pain was the most common clinical manifestation in the non-jaundice group. They did not present jaundice due to the complexity of the anatomical structure of ampulla.[2] In the initial stage of tumor growth, the biliary tract relieved the increasing pressure of intra-biliary caused by tumor mass local blocking by strengthening the emptying function and compensatory dilatation. The biliary tract had not been completely obstructed at this point and did not present jaundice. Abdominal pain occurred when the tumor invaded nerves of adjacent duodenal, gallbladder and celiac plexus. With the development of the lesions, the degree of abdominal pain could be aggravated. The site of abdominal pain gradually spread from epigastrium to hypogastrium or total abdomen. Patients without jaundice at diagnosis were prone to be underdiagnosed or misdiagnosed as dyspepsia or chronic gastritis owing to atypical clinical symptoms, which led to delay in diagnosis and treatment.[11]

Table 4

Univariate and multivariate survival of all patients with periampullary carcinomas (n = 504).

		Univariate	Multivariate		
Variable	**Comparison**	***P* value**	***P* value**	**HR**	**95% confidence interval**
Age	<65 years vs ≥65 years	.081			
Regular alcohol consumption	No vs Yes	.017			
Abdominal pain	No vs Yes	.031			
CA19-9	<37 U/mL vs ≥37U/mL	.005			
CEA	<5ng/mL vs ≥5ng/mL	.003	<.013	2.567	1.224–5.382
Diagnosis of primary tumor	DC, DCC, AC vs PC	.033			
Cell differentiation	Good, Moderate vs. Poor	<.001	<.001	4.376	2.244–8.535
Pancreatic invasion	No vs Yes	.049			
N-factor	No vs Yes	.053			
M-factor	No vs Yes	.050			
Venous invasion	No vs Yes	.047			
Pancreaticoduodenectomy	Yes vs No	<.001			
Chemotherapy	Yes vs No	.019	<.001	3.475	1.730–6.979
Radiotherapy	Yes vs No	.050			
Recurrence	No vs Yes	.002	.014	2.611	1.213–5.620

Only those variables with a significant association <0.1 in the univariate model were candidates for the multivariate model.

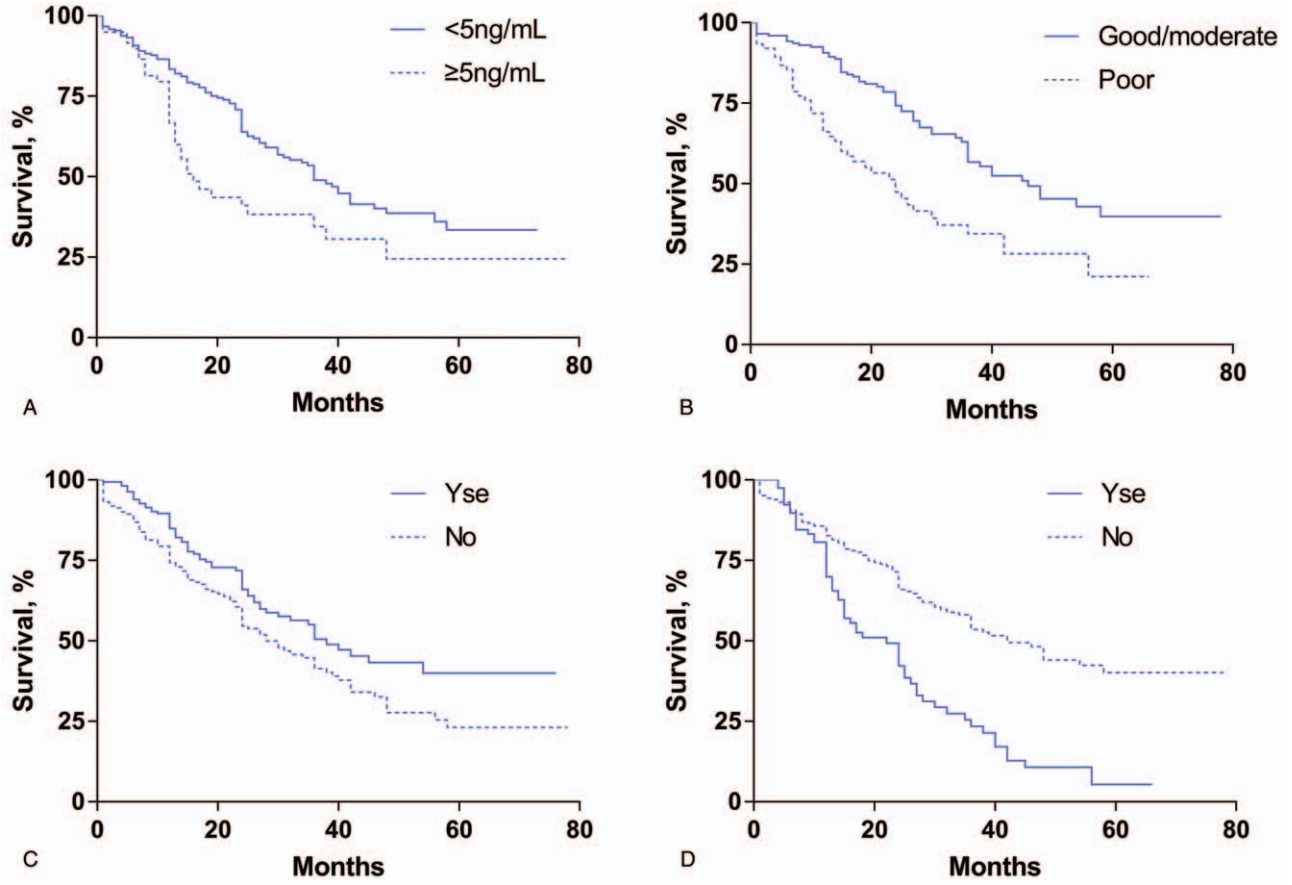

Figure 2. Kaplan–Meier curves showing survival of periampullary carcinomas (A) level of CEA, (B) cell differentiation, (C) chemotherapy, (D) recurrence.

Imaging examination plays a particularly crucial role in localization and qualitative diagnosis of PACs without specific symptoms. US and CT were the most used methods in our study. US was considered to be the first tool for the diagnosis of PACs because of its non-invasive and economy.[11] We could find biliary and pancreatic duct dilatation, hypoechoic masses and hepatic metastases through US. In the non-jaundice group, biliary abnormal dilatation was less common than that in the jaundice group, therefore, detecting tumor masses was the key to diagnosis. But the detection of tumor masses and hepatic metastases was not reliable by US compared with CT. In accordance with the results of our study, the accuracy of diagnosis of CT scanning (78.3%) was comparable with that of MRI/MRCP (73.0%), which lower than that of ERCP (97.4%). Considering the added expense and availability of MRI/MRCP and the risk of procedure-related complications of ERCP, CT was widely used as a requisite procedure in overall diagnosis and staging.[20]

More than half of patients had abnormal level of Hb in both groups according to our results, which may be attributed to gastrointestinal bleeding caused by vascular invasion of tumors.[4] In contrast to patients in the jaundice group, the extent of liver function decline including AST, ALT, γ-GT, and ALP of non-jaundiced patients was significantly lower. A recent study from Japan reported that γ-GT was considered to be the most sensitive marker of hepatocyte releasing enzyme in biliary tract compression thus it could be taken as an essential part in the diagnosis of DCC at a non-jaundice stage.[10] The decrease of serum albumin and pre-albumin was showed in patients of 2 groups may be the result of malnutrition and liver function impairing.[4] CA19-9 increased markedly in both groups of PACs in the present study, particularly in the jaundice group. The previous investigations have demonstrated that CA19-9 was a significant prognostic indicator,[15,21] but our study did not support it because we found no evidence of a significant association between CA19-9 level and survival of patients with PACs by multivariate analysis. Laboratory examinations could be used for closely following up patients of PACs without abnormal presentations on imaging in the non-jaundice stage.

The presentation of jaundice was showed a closely correlation with the size and the primary sites of the tumor. According to the data of our study, the median tumor size was significantly larger in non-jaundice group, which had no difference in both groups in other studies.[9,10,18] We found that DCC was more common in the jaundice group, while PC was more found in non-jaundiced patients because the distal bile duct may not be involved in the early stage which was consistent with the view of Sarmiento et al.[2] Additionally, our study showed that patients in the non-jaundice group were significantly more in the stage I, which was in accordance with that documented in the literatures.[9,10] Kamisawa et al[6] compared 23 patients with non-jaundice ampullary carcinoma and 38 patients with jaundice ampullary carcinoma also concluded that the non-jaundice group included a significantly greater number of carcinomas were in an early stage.

Despite the above findings, pancreatic and perineural invasion were significantly less common among non-jaundiced patients in the present series, which is comparable to previously reported cases.[8,18]

PACs encompassing 4 different anatomical subtypes: pancreatic cancer, biliary cancer, ampullary cancer, and duodenal cancer, which may have different molecular features.[22,23] K-ras is the most frequent mutation of PC, while the non-pancreatic PACs have a lower incidence of K-ras mutation. The relevant targeted therapy showed a trend to improved survival.[23,24] AC are subdivided into intestinal or pancreatobiliary subtype according to the expression of CDX2 and MUC1.[23] A study highlighted the importance of tailoring chemotherapy based on the subgroups of AC, because they have different responsive rates to different chemotherapy regimens.[25] In addition, the detection of molecular alterations could provide basis for surgery or conservative approaches.[26] Therefore, the molecular features and related therapeutic strategies of subtypes of PACs are merited to be studied more in-depth in future.

Surgical resection is the only and most effective curative treatment for PACs.[5,27] Among of them, PD as a radical resection is the standard treatment for patients with resectable PACs.[12,15,28] In our study, the 5-year survival rate of resected PACs was 41.3%, which was consistent with the results reported by previous studies (15%–65%).[4,13,15,29] It was demonstrated that there was no difference between standard PD and pylorus-preserving pancreaticoduodenectomy in survival in a previous study.[27] With the improvements of surgical techniques and progresses in peri- and postoperative care, the postoperative mortality rate in patients who underwent PD for PACs has decreased to less than 5%,[30] which was consistent with our results (4.8%). Patient selection was reported as a vital factor in decreasing postoperative morbidity and mortality.[31] A study from Korea showed postoperative complications presented in 71 of 200 patients with PACs after PD and significantly influenced overall survival and disease-free survival.[19] In the present study, the occurrence rate of postoperative morbidity was 20.5% which lower than the former report and did not show a significant influence on survival by multivariate analysis. Apart from PD, local excision was considered when small tumors (1 cm) were confined to the ampulla of Vater or the distal common bile duct.[2] Patients with advanced tumors or intestinal obstruction were candidates for performing palliative by-pass surgery.

Adjuvant chemotherapy and adjuvant radiotherapy contributing to long-term survival of PACs remain controversial. There was a meta-analysis of adjuvant therapy including 1671 patients showed no associated survival benefit was gained from chemotherapy and radiotherapy in the treatment of PACs.[29] However, several studies demonstrated that "high-risk" features for patients with PACs, which meant T3/T4 primary tumors, positive lymph nodes, poor cell differentiation or positive resection margins, benefited more from adjuvant treatment.[1,32] In the present study, we also found that adjuvant chemotherapy was an independent factor for better overall survival of patients with PACs who underwent PD or not. Neoptolemos et al[33] found that although adjuvant chemotherapy improved survival, the effect was so modest that further study was warranted.

To improve the prognosis of PACs, quite a few researchers have studied manifold factors for predicting outcomes of patients with PACs including preoperative characteristics, tumor-specific factors and treatment-related factors.[1,3,12–15,17,21,28] In our cohort, preoperative CEA level was an independent factor in multivariate analysis which never mentioned in previous studies to our best knowledge. It was reported that CEA was expressed in 73% of DC and in 63% of AC.[34] Suzuki et al[35] concluded from a univariate analysis of patients with DCC that CEA, the body mass index and C-reactive protein were significantly associated with survival. The tumor grade (poor cell differentiation) had a negative effect on overall survival of patients with PACs had been demonstrated in several studies,[7,12,28,33] which was also supported in our study.

In addition, recurrence indicated an unfavorable prognosis for PACs was found in this study. The incidence of recurrence (17.9%) in our study was slightly lower than which reported in previous studies (20%–61%).[17,36] This underestimation could be explained by the fact that the major primary sites in our series were DC and DCC whereas in other studies, PC was the most common tumor site. Furthermore, PC was known as the most aggressive subgroup of PACs. The origin of the tumor as an independent predictor of survival of patients with PACs was demonstrated in several previous investigations.[1,12,13] Nevertheless, it disappeared in our multivariate analysis though it was recognized as a significant prognostic factor in the univariate analysis.

The view that jaundice was an independent prognostic factor was supported by the results of some previous researches,[7,12] while in our study, it failed to be a significant prognosis factor by univariate and multivariate analysis. This finding was likely related to the lower resected rate of PD of the non-jaundice group. Some studies also reported that jaundice had an adverse impact on survival by univariate analysis but was not selected as an independent prognosis factor by multivariate analysis.[8,9,14,28] A previous study from China showed that jaundice was not a reliable criterion for the prediction of the resectability and the extent of tumor progression in patients with DCC.[11] However, patients of the non-jaundice group had a significantly better long-term (≥5 years) survival from our data. Relatively favorable prognosis of non-jaundiced PACs was thought to be related to early stage of tumors and less pancreatic and perineural invasion. Nakata et al[18] reported that the jaundice group tended to a higher recurrence rate of liver metastatic compared to the non-jaundice group of pancreatic head cancer.

There are several limitations in this study. First, it was a retrospective analysis conducted by a single institution. Second, a small number of patients were either missed follow-up or only had a short follow-up time. However, we believe that these limitations did not affect the outcomes of this study significantly because of the striking differences between the 2 groups.

In conclusion, jaundice was not an independent prognostic factor for PACs, but patients in a non-jaundice stage at diagnosis had significantly better clinicopathological features and cumulative 5-year survival than such patients with jaundice. After multivariate analysis, CEA ≥5ng/mL, poor cell differentiation, absence of chemotherapy and presence of recurrence were found to be independent unfavorable factors for overall survival of PACs.

Author contributions

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