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Preoperative Alkaline Phosphatase-to-Cholesterol Ratio as a Predictor of Overall Survival in Pancreatic Ductal Adenocarcinoma Patients Undergoing Radical Pancreaticoduodenectomy

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Background: The value of alkaline phosphatase and cholesterol for predicting overall survival (OS) in cancer patients has been previously studied. However, the predictive value of these variables in patients with pancreatic ductal adenocarcinoma (PDAC) was limited. Hence, we conducted this study to investigate the prognostic value of the alkaline phosphatase-to-cholesterol ratio (ACR) in patients undergoing radical pancreaticoduodenectomy (PD) for PDAC.

Material/Methods: A total of 102 PDAC patients undergoing radical PD at the Cancer Hospital Chinese Academy of Medical Sciences were retrospectively enrolled based on medical records from June 2009 to June 2019. R programming language was used for the optimal cutoff value of biological markers such as preoperative ACR. Kaplan-Meier method and log-rank test were used for univariate survival analysis, and a Cox regression model was used for multivariate survival analysis.

Results: The optimal cutoff value of preoperative ACR was 32.988. Patients with higher preoperative ACR values had worse OS ($P<0.001$). Higher preoperative ACR was significantly correlated with the degree of tumor differentiation ($P<0.018$); levels of alanine aminotransferase ($P<0.001$), aspartate aminotransferase ($P<0.001$), total bilirubin ($P<0.001$), and carbohydrate antigen 19-9 ($P=0.016$); and clinical symptoms ($P=0.001$). Multivariate analysis showed that tumor differentiation ($P<0.001$), ACR value (hazard ratio [HR]: 2.225, 95% confidence interval [CI]: 1.33-3.724, $P=0.002$), and sex (HR, 1.725, 95% CI: 1.1-2.704, $P=0.018$) were independent factors associated with the prognosis of PDAC patients undergoing radical PD.

Conclusions: The preoperative ACR was correlated with OS in pancreatic cancer patients undergoing radical pancreaticoduodenectomy. Elevated ACR was correlated with poor OS.

Keywords: Alkaline Phosphatase • Cholesterol • Pancreatic Cancer, Adult • Pancreaticoduodenectomy • Predictive Value of Tests

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Background

Pancreatic cancer has the worst prognosis and the highest mortality rate among all malignancies. In China, pancreatic cancer takes sixth place in terms of mortality, with morbidity and mortality rates having increased in recent years [1]. In the United States, it ranks 10th for estimated new male cases, ninth for estimated new female cases, and fourth for estimated deaths among male and female cases, separately. Meanwhile, the 5-year survival rate of confirmed cases is reported to be less than 9%, with about 80%-85% of patients having distant metastases at the time of diagnosis [2]. According to a British study, pancreatic cancer is about to surpass breast cancer and become the third leading cause of death in the European Union [3]. Despite recent advances in pancreatic cancer diagnosis, preoperative management strategies, and surgical levels, no significant progress has been made in increasing the overall survival (OS) time of cancer patients [4]. In addition, a series of studies have been conducted on high-risk factors for pancreatic cancer, such as smoking [5], obesity [6], diabetes [7], and familial predisposition [8], without making any remarkable contribution to early diagnosis. Therefore, simple, economical, and effective predictors of OS time could help manage pancreatic carcinoma patients more efficiently.

Systemic inflammatory and immune responses occupy a key role in the tumorigenesis of many cancers, including pancreatic cancer [9]. Relevant reports have found that alkaline phosphatase (ALP) plays a major role in inflammation by affecting purine signal transduction, which can stop inflammatory signals and thus induce immunosuppression [10]. Furthermore, the predictive value of ALP combined with other biomarkers has been reported in resectable and nonresectable pancreatic carcinoma [11-13]. Additionally, in patients undergoing immunotherapy, higher cholesterol (CHO) levels are known to be associated with a better prognosis [14]. Therefore, ALP and CHO can be jointly used to predict OS in cancer patients.

Nonetheless, the relationship between the ALP-to-CHO ratio (ACR) and the prognosis of patients undergoing radical pancreaticoduodenectomy (PD) has not been investigated so far. Hence, we conducted a retrospective study to assess the predictive value of ACR in patients undergoing radical PD for pancreatic ductal adenocarcinoma (PDAC).

Material and Methods

A total of 102 patients undergoing radical PD for PDAC at the Cancer Hospital Chinese Academy of Medical Sciences between June 2009 and June 2019 were retrospectively analyzed. Patients with a previous or current medical history of other malignant tumors, as well as those with hepatitis who had received neoadjuvant therapy before surgery, were excluded.

Data Collection

For each patient, the following data were collected: age; sex; body mass index; laboratory test results, including white blood cell (WBC) counts and plasma levels of alanine aminotransferase, aspartate transaminase, total bilirubin, albumin, globulin, carbohydrate antigen 19-9 (CA19-9), ALP, and CHO; clinical symptoms; history of diabetes, smoking, drinking, and familial predisposition to cancer; and tumor characteristics, including tumor differentiation, lymphovascular invasion, perineural invasion, capsular invasion, maximum tumor diameter, T-staging, N-staging, tumor-node-metastasis (TNM) staging, and adjuvant therapy. TNM staging was determined based on the pathology report. ACR was defined as ALP divided by CHO.

Ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki published by the World Medical Association (July 9, 2018) and was approved by the Medical Ethics Committee of the National Cancer Center/Cancer Hospital Chinese Academy of Medical Sciences (approval No. 17-168/1424). All patients signed written informed consent forms before enrollment.

Treatment and Follow-Up

All patients received radical PD following admission and were postoperatively followed up every 3 months for the first 2 years and every 6 months thereafter through outpatient medical records and telephone calls. The findings from physical examination and laboratory tests were recorded in detail. OS was calculated from the day of surgery to the date of death or last follow-up (ie, October 15, 2020).

Data Analysis

Normally distributed data are expressed as mean ±standard deviation, nonnormally distributed data as median (minimum-maximum), and categorical variables as frequency and percentage. SPSS 26.0 was used for data analysis, and the optimal cutoff value was calculated using the R programming language (4.0.3). Chi-square test and independent samples *t* test were employed to analyze baseline clinicopathological features. Kaplan-Meier method and log-rank test were utilized for univariate survival analysis. The significant factors identified in the univariate analysis were further examined using a Cox regression model for multivariate survival analysis. *P* value <0.05 waL1 s considered statistically significant.

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Table 1. Baseline characteristics of 102 pancreatic ductal adenocarcinoma patients who underwent radical pancreaticoduodenectomy, n (%).

Characteristic	Patients (n=102)
Age (year)	59 (31-77)
>60	44 (43.1)
≤60	58 (56.9)
Sex	
Male	47 (46.8)
Female	55 (53.9)
Body mass index (kg/m^2)	22.3 (17.4-31.9)
>26.8	14 (13.7)
≤26.8	88 (86.3)
White blood cell (10^9/L)	5.7 (2.8-25.8)
>4.33	86 (84.3)
≤4.33	16 (15.7)
Alanine aminotransferase (U/L)	68.5 (9.0-805.0)
>15.55	89 (87.3)
≤15.55	13 (12.7)
Aspartate aminotransferase (U/L)	53 (10.0-868.0)
>25.5	74 (72.5)
≤25.5	28 (27.5)
Total bilirubin (umol/L)	59.8 (3.6-419.5)
>141.4	35 (34.3)
≤141.4	67 (65.7)
Albumin (g/L)	40.6 (23.2-53.1)
>40.55	52 (50.8)
≤40.55	50 (49.2)
Globulin (g/L)	25.3 (1.9-209.0)
>25.05	59 (57.8)
≤25.05	43 (42.2)
Carbohydrate antigen 19-9 (U/ml)	189.5 (1.0-4839.0)
>117.95	70 (68.6)
≤117.95	32 (31.4)
Clinical symptoms	
Absent	14 (13.7)
Present	88 (86.3)
Diabetes	
Absent	75 (73.5)
Present	27 (26.5)
Hypertension	
Absent	81 (79.4)
Present	21 (20.6)
Smoking status	
Absent	69 (67.6)
Present	33 (32.4)
Alcohol consumption	
Absent	76 (74.6)
Present	16 (15.7)
Family history of cancer	
Absent	99 (97.1)
Present	3 (2.9)
ASA	
1	2 (2.0)
2	84 (82.4)
3	16 (15.7)
Degree of differentiation	
Poorly	11 (10.8)
Moderately	85 (83.3)
Well	6 (5.9)
Lymphovascular invasion	
Absent	65 (63.7)
Present	37 (36.3)
Perineural invasion	
Absent	20 (19.6)
Present	82 (80.4)
Capsular invasion	
Absent	30 (29.4)
Present	72 (70.6)
Maximum tumor diameter (cm)	
>4	14 (13.7)
≤4	88 (86.3)

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Table 1 continued. Baseline characteristics of 102 pancreatic ductal adenocarcinoma patients who underwent radical pancreaticoduodenectomy, n (%).

Characteristic	Patients (n=102)
T stage	
T1	15 (14.7)
T2	73 (71.6)
T3	14 (13.7)
N stage	
N0	53 (52)
N1	33 (32.4)
N2	16 (15.7)
TNM stage	
1	41 (40.2)
2	45 (44.1)
3	16 (15.7)
Adjuvant therapy	
Absent	49 (48)
Present	53 (52)
Preoperative plasma alkaline phosphatase (U/L)	207.0 (43.0-1385.0)
>108.5	72 (70.6)
≤108.5	30 (29.4)
Preoperative plasma cholesterol (mmol/L)	4.7 (2.3-12.5)
>3.49	80 (78.4)
≤3.49	22 (21.6)
Preoperative ACR	45.0 (9.0-325.9)
>32.988	68 (66.7)
≤32.988	34 (33.3)

ACR – alkaline phosphatase/cholesterol ratio.

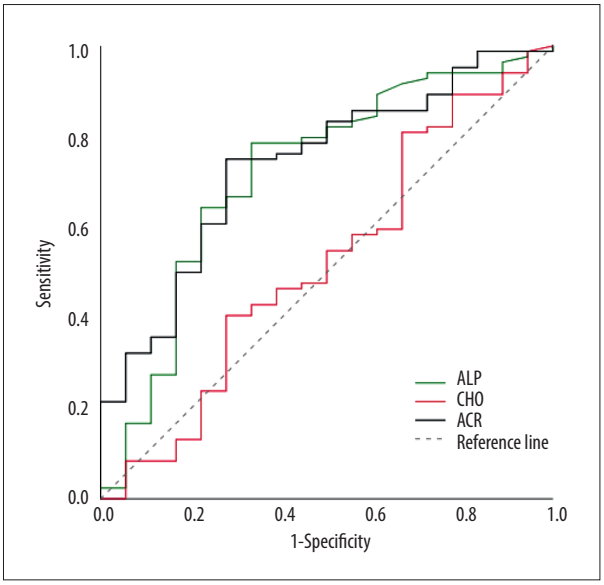

Figure 1. Receiver-operating characteristic (ROC) curve analysis based on preoperative alkaline phosphatase (ALP) concentration, cholesterol (CHO) level, and ALP/CHO ratio (ACR) for overall survival. The area under the ROC curve (AUC) indicates the diagnostic power of ALP, CHO, and ACR. The optimum cutoff point for ALP concentration was 108.5 U/L, and AUC was 0.719 (95% confidence interval [CI], 0.578-0.859), with a sensitivity of 78.6% and a specificity of 33.3% by the Youden index. The optimum cutoff point for CHO level was 3.49 mmol/L, and AUC was 0.521 (95% CI, 0.365-0.678), with a sensitivity of 81.0% and a specificity of 66.7% by the Youden index. The optimum cutoff point for ACR was 32.988, and AUC was 0.737 (95% CI, 0.615-0.859), with a sensitivity of 75.0% and a specificity of 27.8% by the Youden index.

Results

In total, 102 patients (47 men and 55 women) treated with radical PD for PDAC at the Cancer Hospital Chinese Academy of Medical Sciences between June 2009 and June 2019 were included in this retrospective study. The median follow-up time was 14.98 (2.07-106.73) months. A total of 84 patients died during the follow-up period. The median follow-up time was 11.07 (2.07-71.70) months. The estimated survival rates at 1, 2, 3, and 5 years were 51.2%, 25%, 10.7%, and 2.4%, respectively.

The median age at the time of diagnosis was 59 (31-77) years, with 44 patients (43.1%) being over 60 years and 58 (56.9%) younger than 60 years. In addition, 88 patients (86.3%) had clinical symptoms at the time of treatment. In 85 cases (83.3%), the tumor was pathologically diagnosed as moderately differentiated carcinoma. According to the TNM staging system, 41

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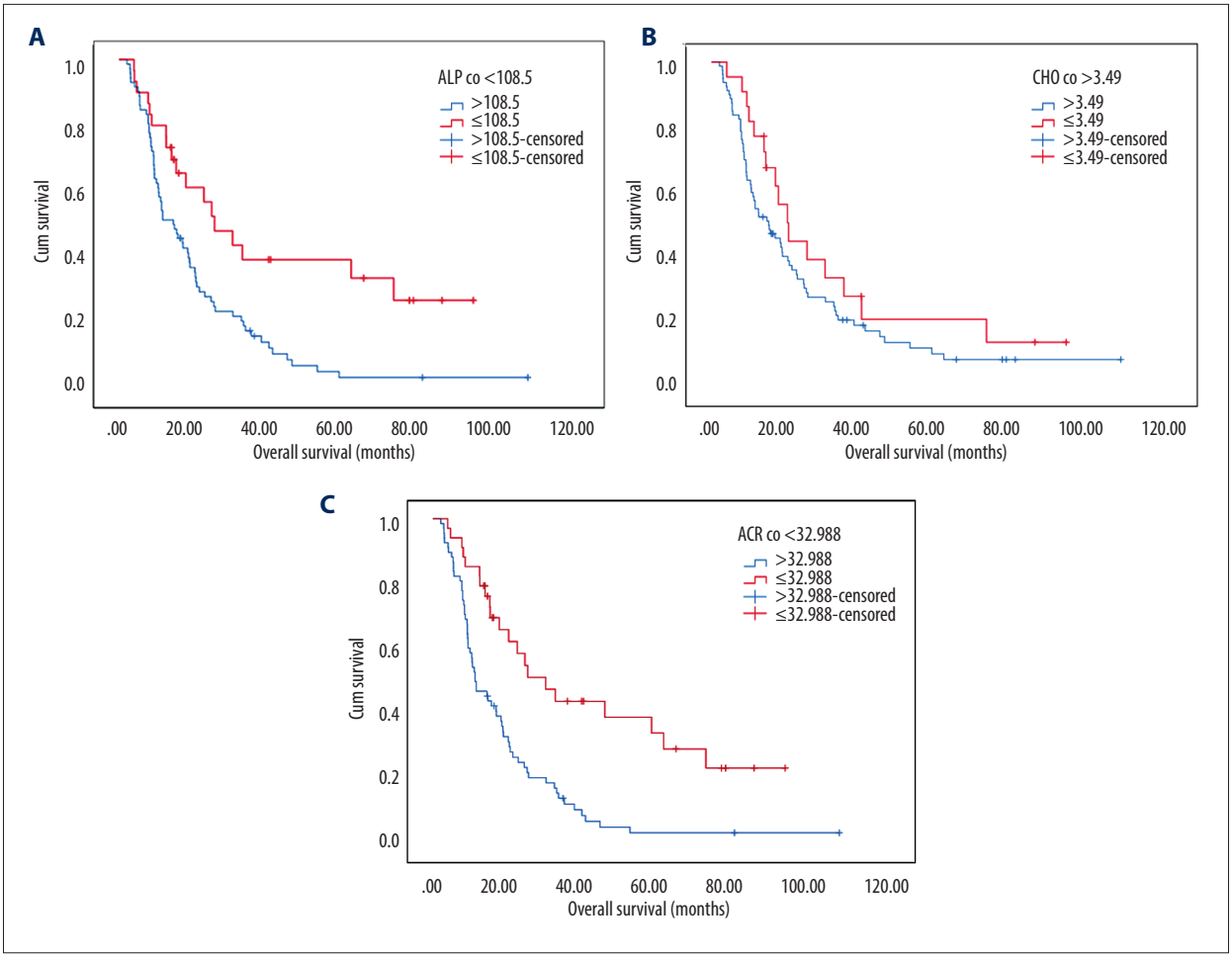

Figure 2. Kaplan-Meier curves generated by preoperative alkaline phosphatase (ALP) concentration, cholesterol (CHO) level, and ALP/CHO ratio (ACR) using the optimal cutoff values. (**A**) In the comparison of preoperative ALP concentration >108.5 U/L with preoperative ALP concentration ≤108.5 U/L (P<0.05), the blue line represents the >108.5 U/L group and the red line represents the ≤108.5 U/L group. (**B**) In the comparison of preoperative cholesterol level >3.49 mmol/L and preoperative cholesterol level ≤3.49 mmol/L (P=0,181), the blue line represents the >3.49 mmol/L group and the red line represents the ≤3.49 mmol/L group. (**C**) In the comparison of preoperative ACR >32.988 with preoperative ACR ≤32.988 (P<0.05), the blue line represents the ACR >32.988 group and the red line represents the ACR ≤32.988 group.

patients (40.2%) were classified as stage I, 45 (44.1%) as stage II, and 16 (15.7%) as stage III. Postoperative adjuvant chemotherapy was administered to 53 patients (52%) (**Table 1**).

Determination of Optimal Cutoff Values for Survival Analysis

The optimal cutoff values of ALP, CHO, and ACR were calculated by the R programming language to be 108.5 U/L, 3.49 mmol/L, and 32.988, respectively.

The median ACR for all patients in this study was 45.0 (9.0-325.9) (**Table 1**). As is shown in **Figure 1**, the area under the receiver-operating characteristics curve of preoperative ACR is 0.737 (95% confidence interval [CI]: 0.615-0.859), which is higher than ALP (0.719, 95% CI: 0.578-0.859) and CHO (0.521, 95% CI: 0.365-0.678), with 75.0% sensitivity and 27.8% specificity. Based on this optimal cutoff value, 34 patients had a preoperative ACR ≤32.988, and 68 patients had a preoperative ACR >32.988, as detailed in **Table 1**. The survival curve for preoperative ACR reveals that the OS of patients with ACR > 32.988 was shorter than that of patients with ACR ≤0.08 (**Figure 2**).

ACR Correlation Analysis

Based on the best cutoff value of preoperative ACR, patients were divided into 2 groups, namely, low ACR (≤32.988) and high ACR (>32.988). High preoperative ACR values were found to be significantly correlated with alanine aminotransferase (P=0.001), aspartate transaminase (P=0.001), total bilirubin

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Table 2. Correlation between preoperative alkaline phosphatase-to-cholesterol ratio (ACR) and clinicopathological characteristics in pancreatic ductal adenocarcinoma patients who underwent radical pancreaticoduodenectomy, n (%).

Characteristic	Preoperative ACR		P value
	>32.988 (n=68)	≤32.988 (n=34)	
Age (year)			0.888
>60	29 (28.4)	15 (14.7)	
≤60	39 (38.2)	19 (18.6)	
Sex			0.482
Male	33 (32.4)	14 (13.7)	
Female	35 (34.3)	20 (19.6)	
Body mass index (kg/m^2)			0.416
>26.8	8 (7.8)	6 (5.9)	
≤26.8	60 (58.8)	28 (27.5)	
White blood cell (10^9/l)			0.124
>4.33	60 (58.8)	26 (25.5)	
≤4.33	8 (7.8)	8 (7.8)	
Alanine aminotransferase (U/l)			0.001
>15.55	66 (64.7)	23 (22.5)	
≤15.55	2 (2.0)	11 (10.8)	
Aspartate aminotransferase (U/l)			0.001
>25.5	61 (59.8)	13 (12.7)	
≤25.5	7 (6.9)	21 (20.6)	
Total bilirubin (umol/l)			0.001
>141.4	33 (32.4)	2 (2.0)	
≤141.4	35 (34.3)	32 (31.4)	
Albumin (g/l)			0.05
>40.55	30 (29.4)	22 (21.6)	
≤40.55	38 (37.3)	12 (11.8)	
Globulin (g/l)			0.119
>25.05	43 (42.2)	16 (15.7)	
≤25.05	25 (24.5)	18 (17.6)	
Carbohydrate antigen 19-9 (U/ml)			0.016
>117.95	52 (51)	18 (17.6)	
≤117.95	16 (15.7)	16 (15.7)	
Clinical symptoms			0.001
Absent	3 (2.9)	11 (10.8)	
Present	65 (63.7)	23 (22.5)	

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Table 2 continued. Correlation between preoperative alkaline phosphatase-to-cholesterol ratio (ACR) and clinicopathological characteristics in pancreatic ductal adenocarcinoma patients who underwent radical pancreaticoduodenectomy, n (%).

Characteristic	Preoperative ACR		P value
	>32.988 (n=68)	≤32.988 (n=34)	
Diabetes			0.634
Absent	49 (48)	26 (25.5)	
Present	19 (18.6)	8 (7.8)	
Hypertension			0.603
Absent	53 (52.0)	28 (27.5)	
Present	15 (14.7)	6 (5.9)	
Smoking status			0.748
Absent	50 (49.0)	26 (25.5)	
Present	18 (17.6)	8 (7.8)	
Alcohol consumption			0.851
Absent	57 (55.9)	28 (27.5)	
Present	11 (10.8)	6 (5.9)	
Family history of cancer			0.214
Absent	67 (65.7)	32 (31.4)	
Present	1 (1.0)	2 (2)	
ASA			0.145
1	1 (1.0)	1 (1.0)	
2	53 (52)	31 (30.4)	
3	14 (13.7)	2 (2.0)	
Degree of differentiation			0.018
Poorly	9 (8.8)	2 (2.0)	
Moderately	58 (56.9)	27 (26.5)	
Well	1 (1.0)	5 (4.9)	
Lymphovascular invasion			0.467
Absent	45 (44.1)	20 (19.6)	
Present	23 (22.5)	14 (13.7)	
Perineural invasion			0.86
Absent	13 (12.7)	7 (6.9)	
Present	55 (53.9)	27 (26.5)	
Capsular invasion			0.167
Absent	17 (16.7)	13 (12.7)	
Present	51 (50)	21 (20.6)	

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Table 2 continued. Correlation between preoperative alkaline phosphatase-to-cholesterol ratio (ACR) and clinicopathological characteristics in pancreatic ductal adenocarcinoma patients who underwent radical pancreaticoduodenectomy, n (%).

Characteristic	Preoperative ACR		P value
	>32.988 (n=68)	≤32.988 (n=34)	
Maximum tumor diameter (cm)			0.416
>4	8 (7.8)	6 (5.9)	
≤4	60 (58.8)	28 (27.5)	
T stage			0.293
T1	8 (7.8)	7 (6.9)	
T2	52 (51.0)	21 (20.6)	
T3	8 (7.8)	6 (5.9)	
N stage			0.148
N0	34 (33.3)	19 (18.6)	
N1	20 (19.6)	13 (12.7)	
N2	14 (13.7)	2 (2.0)	
TNM stage			0.148
1	25 (24.5)	16 (15.7)	
2	29 (28.4)	16 (15.7)	
3	14 (13.7)	2 (2.0)	
Adjuvant therapy			0.07
Absent	37 (36.3)	12 (11.8)	
Present	31 (30.4)	22 (21.6)	
Preoperative plasma alkaline phosphatase (U/l)			0.001
>108.5	66 (64.7)	6 (5.9)	
≤108.5	2 (2.0)	28 (27.5)	
Preoperative plasma cholesterol (mmol/l)			0.061
>3.49	57 (55.9)	23 (22.5)	
≤3.49	11 (10.8)	11 (10.8)	

ACR – alkaline phosphatase/cholesterol ratio.

(*P*=0.001), CA19-9 (*P*=0.016), clinical symptoms (*P*=0.001), differentiation degree (*P*=0.049), and preoperative serum ALP (*P*=0.001), as detailed in **Table 2**.

Univariate and Multivariate Analyses

Univariate analysis showed that sex (hazard ratio [HR], 1.763; 95% CI, 1.142-2.72; *P*=0.01), preoperative WBC count (HR, 2.541; 95% CI, 1.264-5.109; *P*=0.009), alanine aminotransferase (HR, 3.169; 95% CI, 1.372-7.317; *P*=0.007), total bilirubin (HR, 2.071; 95% CI, 1.314-3.266; *P*=0.002), CA19-9 (HR, 2.043; 95% CI, 1.236-3.375; *P*=0.005), degree of differentiation (poorly vs well, HR=15.113, 95% CI, 3.99-57.239; moderately/well, HR=4.6, 95% CI=1.437-14.724), adjuvant therapy (HR, 1.55; 95% CI, 1.008-2.384; *P*=0.046), preoperative plasma ALP (HR, 2.247; 95% CI, 1.32-3.824; *P*=0.003), and preoperative ACR (HR, 2.609; 95% CI, 1.573-4.327; *P*=0.001) were independent predictors of OS in patients undergoing radical PD (**Table 3**).

In contrast, the following were not determined as independent factors associated with the OS of patients treated with radical PD: age, body mass index, aspartate transaminase,

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Table 3. Univariate analysis for overall survival in pancreatic ductal adenocarcinoma patients who underwent radical pancreaticoduodenectomy.

Characteristic	Categories	Wald	HR* (95% CI**)		P value
Age (year)	>60 vs ≤60	1.23	1.28	(0.827-1.982)	0.267
Gender	Male vs Female	6.558	1.763	(1.142-2.72)	0.01
Body Mass Index (kg/m^2)	>26.8 vs ≤26.8	0.572	0.774	(0.399-1.503)	0.45
White Blood Cell (10^9/l)	>4.33 vs ≤4.33	6.85	2.541	(1.264-5.109)	0.009
Alanine aminotransferase (U/l)	>15.55 vs ≤15.55	7.297	3.169	(1.372-7.317)	0.007
Aspartate aminotransferase (U/l)	>25.5 vs ≤25.5	2.423	1.502	(0.9-2.506)	0.12
Total bilirubin (umol/l)	>141.4 vs ≤141.4	9.831	2.071	(1.314-3.266)	0.002
Albumin (g/l)	>40.55 vs ≤40.55	0.792	0.823	(0.536-1.264)	0.374
Globulin (g/l)	>25.05 vs ≤25.05	0.23	1.437	(0.916-2.254)	0.115
Carbohydrate antigen 19-9 (U/ml)	>117.95 vs ≤117.95	7.777	2.043	(1.236-3.375)	0.005
Clinical symptoms	Absent vs present	3.766	0.526	(0.275-1.006)	0.052
Diabetes	Absent vs present	0.758	0.809	(0.502-1.303)	0.384
Hypertension	Absent vs present	1.809	0.695	(0.409-1.181)	0.179
Smoking status	Absent vs present	0.686	1.226	(0.757-1.983)	0.408
Alcohol consumption	Absent vs present	0.247	1.157	(0.651-2.057)	0.619
Family history of cancer	Absent vs present	0.056	1.185	(0.291-4.832)	0.813
ASA	1 vs 3	0.535	0.571	(0.127-2.562)	0.464
	2 vs 3	2.535	0.623	(0.348-1.115)	0.111
Degree of differentiation	Poorly/well	15.974	15.113	(3.99-57.239)	0.0001
	Moderately/well	6.61	4.6	(1.437-14.724)	0.01
Lymphovascular invasion	Absent vs present	1.242	0.772	(0.491-1.216)	0.265
Perineural invasion	Absent vs present	1.1	0.745	(0.43-1.291)	0.294
Capsular invasion	Absent vs present	3.318	0.635	(0.39-1.035)	0.069
Maximum tumor diameter (cm)	Absent vs present	0.387	0.81	(0.416-1.575)	0.534
T stage	1 vs 3	0.026	0.933	(0.402-2.166)	0.872
	2 vs 3	0.67	1.326	(0.675-2.604)	0.413
N stage	1 vs 3	3.019	0.578	(0.311-1.073)	0.082
	2 vs 3	1.17	0.698	(0.364-1.339)	0.279
TNM stage	1 vs 3	2.994	0.57	(0.301-1.078)	0.084
	2 vs 3	1.506	0.676	(0.361-1.264)	0.22
Adjuvant therapy	Yes vs No	3.989	1.55	(1.008-2.384)	0.046
Preoperative plasma ALP (U/l)	>108.5 vs ≤108.5	8.899	2.247	(1.32-3.824)	0.003
Preoperative plasma CHO (mmol/l)	>3.49 vs ≤3.49	1.762	0.691	(0.4-1.193)	0.184
Preoperative ACR	>32.988 vs ≤32.988	13.796	2.609	(1.573-4.327)	0.0001

HR – hazard ratio; CI – confidence interval; ALP – alkaline phosphatase; CHO – cholesterol ratio; ACR – alkaline phosphatase/cholesterol ratio.

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Table 4. Multivariate analysis for overall survival in pancreatic ductal adenocarcinoma patients who underwent radical pancreaticoduodenectomy.

Variables	Categories	Univariate analysis			Multivariate analysis		
		Wald	P	HR (95.0% CI)	Wald	P	HR (95.0% CI)
Gender	Male vs Female	6.558	0.01	1.763 (1.142-2.72)	5.644	0.018	1.725 (1.1-2.704)
White blood cell (10^9/l)	>4.33 vs ≤4.33	6.85	0.009	2.541 (1.264-5.109)		/	
Alanine aminotransferase (U/l)	>15.55 vs ≤15.55	7.297	0.007	3.169 (1.372-7.317)		/	
Total bilirubin (umol/l)	>141.4 vs ≤141.4	9.831	0.002	2.071 (1.314-3.266)		/	
Carbohydrate antigen 19-9 (U/ml)	>117.95 vs ≤117.95	7.777	0.005	2.043 (1.236-3.375)		/	
Degree of differentiation					14.186	0.0001	
	Poorly/well	15.974	0.0001	15.113 (3.99-57.239)	11.128	0.001	14.724 (3.032-71.494)
	Moderately/well	6.61	0.01	4.6 (1.437-14.724)	4.893	0.027	5.074 (1.203-21.398)
Adjuvant therapy	Absent vs present	3.989	0.046	1.55 (1.008-2.384)		/	
Preoperative plasma ALP (U/l)	>108.5 vs ≤108.5	8.899	0.003	2.247 (1.32-3.824)		/	
Preoperative plasma CHO (mmol/l)	>3.49 vs ≤3.49	1.762	0.184	0.691 (0.4-1.193)		/	
Preoperative ACR	>32.988 vs ≤32.988	13.796	0.0001	2.609 (1.573-4.327)	9.273	0.002	2.225 (1.33-3.724)

HR – hazard ratio; CI – confidence interval; ALP – alkaline phosphatase; CHO – cholesterol ratio; ACR – alkaline phosphatase/cholesterol ratio.

albumin, globulin, clinical symptoms, diabetes, hypertension, smoking status, alcohol consumption, family history of cancer, American Society of Anesthesiologists classification, lymphovascular invasion, perineural invasion, capsular invasion, maximum tumor diameter, T-stage, N-stage, TNM stage, and preoperative CHO level.

In multivariate regression analysis, tumor differentiation degree (P<0.001), sex (HR, 1.725; 95% CI, 1.1-2.704; P=0.018), and preoperative ACR (HR, 2.225; 95% CI, 1.33-3.724; P=0.002) were identified as independent prognosticators in patients undergoing radical PD (**Table 4**).

Discussion

Our results demonstrated that preoperative ACR was an independent predictor of OS in PDAC patients undergoing radical PD, with higher ACR values correlating with a worse prognosis. To our knowledge, this report is the first on the relationship between ACR and the prognosis of PDAC patients undergoing radical PD. Furthermore, multivariate analysis indicated that sex (P=0.016), preoperative WBC count (P=0.049), tumor differentiation degree (P=0.001), and preoperative ACR (P=0.017) were associated with the prognosis of these patients.

Despite being a currently accepted cancer staging system, TNM classification has been shown to have limited ability in cancer staging prediction [15]. A number of studies have focused on the predictors of OS in various tumors, including pancreatic carcinoma. For example, patients with a high neutrophil-to-lymphocyte ratio in the early stage of pancreatic cancer have been reported have poorer OS compared with those with a low neutrophil-to-lymphocyte ratio [16]. In addition, the prognosis of pancreatic carcinoma patients with a high glucose/lymphocyte ratio has been estimated to be worse than that of patients with a low glucose/lymphocyte ratio [17]. Another study has identified high serum albumin levels as a protective

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prognostic factor in advanced pancreatic carcinoma patients treated with gemcitabine and albumin-bound paclitaxel [18]. However, the predictive value of combined ALP and CHO in pancreatic carcinoma has not been studied yet.

ALP is an enzyme secreted by the liver and released from the biliary tract. It belongs to a protein superfamily [19], and it is widely distributed throughout the body and mainly found in skeletal muscles, intestine, kidney, and liver. Oxidative stress has been suggested to increase the activity of ALP and its sensitivity to levamisole, homoarginine, and heat in cells [20]. Tumors in the head of the pancreas can cause bilirubin stasis, which in turn leads to abnormal liver function and changes in serum ALP levels.

Studies have reported that ALP can improve tumor cell invasion, metastasis, and proliferation ability [21]. It has also been identified as a predictor of bone metastasis in both lung and kidney cancer patients, with higher ALP levels capable of promoting tumor bone metastasis [22,23]. Moreover, higher ALP levels have been demonstrated to serve as a risk factor for lymph node metastasis in esophageal cancer [24], correlate with a later stage in colon cancer [25], and promote cell invasion and metastasis in pancreatic carcinoma; whereas, decreased ALP activity can reportedly inhibit tumor cell metastasis and invasion [26]. Other studies have indicated that the ratios of ALP to serum albumin and ALP to lactate dehydrogenase might predict the OS of patients with resectable and unresectable pancreatic carcinoma, respectively [11,12].

CHO is an important raw material for the synthesis of physiological activators, such as adrenal cortex hormones, sex hormones, bile acids, and vitamin D. It is also the main component of cell membranes, and its serum concentration can be used as an indicator of lipid metabolism [27]. Recently, it was discovered that the PCSK9 protein, which regulates CHO metabolism, has immune regulation functions for tumors, and that inhibiting its activity can promote the intratumoral infiltration of cytotoxic T cells and thereby enhance the effect of immunotherapy [28]. In another study, it was found that the positive regulation of CHO levels could change the invasive and metastatic capabilities of mouse ovarian cancer cells, and that patients with higher serum CHO levels were more sensitive to immunosuppressive agents for tumors [29]. CHO has also been shown to downregulate interleukin-9-mediated $CD8^+$ T-cell differentiation and antitumor activity [30]. Inhibition of CHO acyltransferase can promote the proliferation of $CD8^+$ T cells, which might play a central role in antitumor immunity [31]. The antitumor effect of CHO has been confirmed in breast cancer, kidney cancer, and soft tissue sarcoma [32-34]. Additionally, a meta-analysis involving 24,655 patients confirmed CHO as a protective factor in patients with cancer [35].

Therefore, preoperative ACR, as an indicator reflecting both preoperative ALP and CHO concentrations, could simultaneously combine their roles in tumor genesis and progression. Compared with a single biomarker, ACR was better able to predict OS in patients undergoing radical PD for PDAC in the current study. Hence, ACR could be used as a prognosticator in PDAC patients undergoing radical PD.

There are some limitations in this study. First, it was a single-center retrospective study with a small sample size, which makes the study prone to selection bias. It will be necessary to design more scientific, multi-center, large-sample prospective studies to verify the conclusions drawn here. Second, due to the small number of patients, patients were not divided into training and experimental groups for statistical verification, and external verification was unavailable, which necessitates further study. Third, the predictive value of preoperative ACR was focused in this study, without taking into account the relationship between postoperative ACR changes and the prognosis of the patients. Finally, during follow-up, many patients received other treatments due to tumor recurrence, which affected OS.

Conclusions

In conclusion, this study, for the first time, proved the prognostic value of preoperative ACR for predicting OS after radical PD for PDAC. Moreover, ACR was shown to be a simple, easy-to-accept, and low-cost factor that could be used as a prognosticator in patients undergoing radical PD for pancreatic head ductal adenocarcinoma. This finding suggests that treatment plans should consider not only TNM stage but also the preoperative serum enzymes, making individualized therapy possible for patients with PDAC. However, the exact mechanisms and function of ALP and CHO in PDAC should be elucidated. Further research is needed to verify the findings of our study.

Conflict of Interest

None disclosed.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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