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The Prognostic Significance of the CALLY Index in Ampullary Carcinoma: An Inflammation-Nutrition Retrospective Analysis

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Background: As a novel inflammatory-nutritional biomarker, the C-reactive protein–albumin–lymphocyte (CALLY) index has demonstrated significant prognostic value in various malignancies. However, research on its association with the prognosis of ampullary carcinoma (AC) is rare. This study aims to investigate the relationship between the CALLY index and the prognosis of patients with AC.

Methods: We retrospectively analyzed data from 201 patients with AC at Sun Yat-sen University Cancer Center. Several clinico-pathological factors and biomarkers were included in the study. Univariate and multivariate Cox regression analyses, along with competing risk analysis, were performed to identify prognostic factors for AC after pancreaticoduodenectomy (PD). Only factors with significant results in univariate analysis were included in multivariate analysis. To ensure the robustness of our findings, propensity score matching (PSM) analyses were conducted to assess survival differences according to the CALLY index.

Results: The univariate and multivariate Cox regression analyses revealed that pathological type, N stage, T stage, postoperative chemotherapy regimen, and the CALLY index were all statistically significant prognostic factors for patients with AC after PD (all P values < 0.05). Taking into account non-cancer-related mortality as competing hazards, these factors remained significant predictors (all P values < 0.05). After PSM, the survival advantage observed between the low and high CALLY groups remained discernible and consistent.

Conclusion: This study indicated that a reduced CALLY index correlates with a poorer cancer-specific survival in AC patients after PD, highlighting its utility as a prognostic marker for this condition.

Keywords: ampullary carcinoma, prognosis, inflammation-nutritional-index, competing risk analysis, propensity matching analysis

Introduction

Ampullary carcinoma (AC) is a rare neoplasm arising from the ampulla of Vater, representing merely 0.2% of gastrointestinal malignancies and 6–20% of periampullary cancers.[1] Generally, AC presents with jaundice symptoms in the early stage due to bile duct obstruction, resulting in a more higher resection rate and more favorable prognosis compared to other periampullary cancers.[2] At present, the predominant therapeutic approach for AC is radical surgical intervention, primarily pancreaticoduodenectomy.[3] Research indicates that the initial surgical resection rate for patients diagnosed with AC stands at approximately 50%,[3] in stark contrast to the rate of approximately 15–20% for those diagnosed with pancreatic cancer.[4] Despite a high incidence of surgical removal, the overall postoperative survival rate

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remains unsatisfactory, with a 5-year survival rate ranging between 35% and 50%.[1,5] Hence, a more refined evaluation of the survival risk in AC holds paramount importance for guiding clinical decision-making processes.

Given the rarity of this cancer and the restricted scope of clinical research cohorts, the prognosis for patients with AC varies significantly across studies due to a range of factors, such as gender, age, TNM stage, lymph node metastasis and vascular invasion, tumor differentiation, and CA19-9 level.[6–9] Recently, the impact of the inflammatory and nutritional status on tumor prognosis is becoming increasingly acknowledged. Previous studies have shown that inflammation exerts significant influence throughout the various phases of tumor progression, encompassing the stages of onset, promotion, malignant conversion, invasion, and metastasis.[10] Additionally, nutritional status is crucial for the prognosis of cancer patients. Due to the metabolic demands of malignant tumors, the loss of appetite, and compromised digestive and absorptive functions, cancer patients are often susceptible to malnutrition, which can lead to a poorer prognosis.[11] Several inflammatory and nutritional biomarkers, such as prognostic nutrition index (PNI),[11,12] neutrophil-to-lymphocyte ratio (NLR),[11] CA19-9 to gamma-glutamyl transpeptidase ratio (CGR),[13] Geriatric nutritional risk index (GNRI),[14] aggregate systemic inflammation index (AISI)[15] and systemic inflammation response index (SIRI),[16] have been demonstrated to be associated with the prognosis of various cancers. Recently, a novel biomarker known as the CALLY index, which comprises C-reactive protein (CRP), albumin, and lymphocyte levels, has demonstrated its significance in comprehensively reflecting a patient's inflammatory status, nutritional status, and immune status, and the index has showed significant prognostic value in various malignancies.[17–20] However, research on the relationship between the CALLY index and the prognosis of AC are rare.

In this research, we explored the correlation between the CALLY index and the clinical outcomes in individuals diagnosed with AC. The purpose of this research was to analyze the various factors that could possibly impact the prognosis in patients with AC who underwent PD from an inflammation-nutritional perspective.

Methods

Patient Enrollment

A total of 201 cases of patients with AC who underwent PD at the Sun Yat-sen University Cancer Center (SYSUCC) during the period from June 2009 to July 2023 have been included in our study. The eligibility criteria for inclusion are: 1) Patients undergoing pancreatoduodenectomy at our institution; 2) Confirmation of AC diagnosis based on postoperative pathology; 3) Patients 18 years of age and above; 4) Complete and accessible follow-up data. The primary exclusion criteria for this study encompass the following: 1) Postoperative pathological examination revealing a diagnosis other than AC; 2) Death occurring within the perioperative period; 3) Unavailability of comprehensive follow-up data. The retrospective study adhered to Helsinki ethics, gained approval from the Ethics Committee of SYSUCC (No. C2021-003-X02), exempted informed consent due to retrospective design, and ensured patient confidentiality through data anonymization.

Medical Data Extraction

By leveraging the electronic medical record system, we extracted medical data of selected patients, encompassing their baseline demographic profiles (age, gender, height, weight), tumor-specific pathological characteristics (tumor diameter, differentiation grade, microvascular and neural invasion status, number of dissected lymph nodes, N / T stages according to the 8th TNM staging system), preoperative laboratory evaluations (spanning CEA, CA19-9, neutrophil, lymphocyte, monocyte counts, albumin levels, c reactive protein), and postoperative adjuvant treatment strategies. We conducted a thorough examination to evaluate the links between preoperative inflammation-nutritional biomarkers namely CGR, GNRI, PNI, CALLY, SIRI, AISI, NLR, and the outcome of AC patients post-PD. Definitions for these markers could be found in the Supplementary Table 1.

Upon discharge, all patients underwent regular outpatient or telephone follow-up, with the conclusion of the follow-up period set as December 31, 2023. The definition of overall survival (OS) refers to the time from surgery until death from any cause or censorship at the date of the last follow-up. The definition of cancer-specific survival (CSS) refers to the time from surgery until death specifically attributed to cancer. In this study, all non-ampullary carcinoma-specific deaths were defined as competing risk events.

Statistical Analysis

Data analysis and interpretation were performed utilizing IBM SPSS Statistics v25.0, MedCalc v19.0.4 and R v4.1.3. A p-value of <0.05 in a two-tailed test indicated statistical significance. For continuous variables, the presentation format is determined by the distribution of their data, with mean ± standard deviation utilized when appropriate, or median with interquartile range when necessary. For categorical variables, they are represented in the form of frequency counts and percentages. Additionally, in this research, we employed the median value as a threshold to categorize preoperative inflammation-related nutritional biomarkers into high and low value groups. For the purpose of comparing categorical variables across groups, we utilized either the chi-square test or Fisher's exact test, depending on the appropriateness of the statistical assumptions. Utilizing the "Forward: LR" approach, a multivariate Cox regression analysis was subsequently conducted, incorporating significant univariate variables identified via the "Stepwise" method. To identify significant variations in prognosis among different groups, we employed the Log rank test to scrutinize the Kaplan-Meier survival analysis. For the competing risk analysis, we first utilized the Fine and Gray approach to assess the sub-hazard ratio for long-term outcome, considering non-ampullary carcinoma-specific deaths as a competing factor. Then, variables found significant in the univariate analysis were subjected to multivariate analysis using the "cmprsk" package in R. We mitigated selection bias by using propensity-matching, calculating scores via logistic regression, and applying nearest-neighbor matching without replacement to achieve a 1:1 cohort matching ratio (caliper=0.2 SD) to balance groups on imbalanced variables. The variables selected for the matching process were those factors exhibiting imbalance between the groups.

Results

Clinicopathological Characteristics

In this study, we included 201 patients with AC who underwent PD. Their clinicopathological characteristics are detailed in Table 1. Among them, 127 (63.2%) were male. The median age of all patients was 59.12 years, with an average tumor diameter of 2.5cm. The majority of tumors were classified as well to moderately undifferentiated. In terms of pathological types, the majority of patients (61.2%) were categorized as the pancreatobiliary type and 24 patients

Table 1 Baseline Data of Ampullary Carcinoma Patients Undergoing Pancreatoduodenectomy

Variables	Total (n=201, %)	Variables	Total (n=201, %)
Age (years)	59.12 ± 0.68	N stage	
Gender		N0	119 (59.2)
Female	74 (36.8)	N1	61 (30.3)
Male	127 (63.2)	N2	21 (10.4)
Tumor Diameter (cm)	2.5 (1.8, 3)	T stage	
Pathological Grade		T1/2	76 (37.8)
Well to moderately	114 (56.7)	T3/4	125 (62.2)
Poorly to undifferentiated	87 (43.3)	Chemotherapy	
Pathological Type		No	66 (32.8)
Pancreatobiliary	123 (61.2)	S-1 based regimen	69 (34.3)
Intestinal	42 (20.9)	Gemcitabine based regimen	31 (15.4)
Mixed	12 (6.0)	Others	35 (17.4)
Others	24 (11.9)	CA 19–9 (U/mL)	118 (32.1, 425.9)

(*Continued*)

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Table 1 (Continued).

Variables	Total (n=201, %)	Variables	Total (n=201, %)
MVI		CEA (ng/mL)	3.2 (2.1, 5.0)
Absence	116 (57.7)	CGR	0.4 (0.1, 2)
Presence	85 (42.3)	GNRI	100.4 ± 0.7
Nerve invasion		PNI	47.4 ± 0.5
Absence	103 (51.2)	CALLY	0.7 (0.2, 2.2)
Presence	98 (48.8)	SIRI	1.5 (0.9, 3.2)
Lymph nodes examination		AISI	456.9 (240.7, 1052.2)
≤ 15 nodes	69 (34.3)	NLR	3.0 (2.1, 5.0)
> 15 nodes	132 (65.7)		

Abbreviations: MVI, microvascular invasion; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; CGR, CA19-9 to gamma-glutamyl transpeptidase ratio; GNRI, Geriatric nutritional risk index; PNI, prognostic nutrition index; CALLY, C-reactive protein-albumin-lymphocyte index; SIRI, systemic inflammation response index; AISI, aggregate systemic inflammation index; NLR, neutrophil to lymphocyte ratio.

(11.9%) were categorized as others (mucinous adenocarcinoma, villous adenocarcinoma, and neuroendocrine tumor). The majority of patients were at T3/4 stage. Overall, microvascular invasion was observed in 85 patients (42.3%), nerve invasion in 98 (48.8%), and lymphatic metastasis in 82 (40.7%). After surgery, the majority of patients (34.3%) received gemcitabine-based chemotherapy as an adjuvant treatment and 35 patients (17.4%) received other chemotherapy regimen (Oxaliplatin, Cisplatin or others).

Prognostic Survival Analyses for AC After PD

The median OS of the selected cohorts was 46.3 months (range: 1.97 to 147.5 months), while the median CSS was 60.0 months (range: 1.97 to 147.5 months, Figure 1a). The OS probabilities at 1 year, 3 years, and 5 years were 93.3%, 60.6%, and 44.3%, respectively. Correspondingly, the CSS probabilities at 1 year, 3 years, and 5 years were 93.3%, 64.0%, and 49.3%, respectively. Results from the multivariate Cox regression analysis indicated that pathological type, N stage, T stage, postoperative chemotherapy regimen, and the CALLY index were significant prognostic factors for patients with AC after PD ($P < 0.05$, Table 2). After accounting for non-cancer-specific mortality in the multivariate competing risk regression analysis, the pathological type, N stage, T stage, postoperative chemotherapy regimen, and the CALLY index remained significant predictors ($P < 0.05$, Table 3).

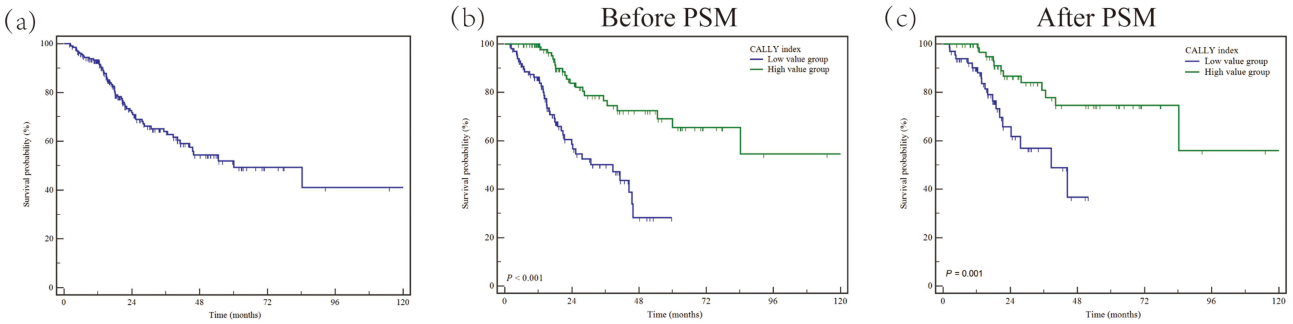

Figure 1 Cancer-specific survival analysis for ampullary carcinoma patients undergoing pancreatoduodenectomy, depicted through Kaplan-Meier curves. Plots of Kaplan-Meier curves estimating cancer-specific survival for total cohort (**a**). Plots of Kaplan-Meier curves estimating cancer-specific survival stratified by CALLY index before (**b**) and after (**c**) PSM.

Table 2 Results of Cox Regression Analysis for Ampullary Carcinoma After Pancreaticoduodenectomy

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age				
≤ 65 years	Ref.	-	-	-
> 65 years	0.91 (0.55–1.52)	0.730	-	-
Gender				
Female	Ref.	-	-	-
Male	1.19 (0.72–1.95)	0.500	-	-
Tumor Diameter				
≤ 2 cm	Ref.	-	-	-
2 cm - 5cm	1.18 (0.67–2.08)	0.568	-	-
> 5cm	4.82 (1.85–12.53)	0.001	-	-
Pathological Grade				
Well to moderately	Ref.	-	-	-
Poorly to undifferentiated	2.02 (1.23–3.33)	0.006	-	-
Pathological Type				
Pancreatobiliary	Ref.	-	Ref.	-
Intestinal	0.44 (0.22–0.86)	0.017	0.27 (0.12–0.57)	< 0.001
Mixed	0.67 (0.21–2.15)	0.497	0.58 (0.17–1.97)	0.379
Others	0.67 (0.30–1.48)	0.318	1.17 (0.5–2.77)	0.717
MVI				
Absence	Ref.	-	-	-
Presence	1.89 (1.17–3.05)	0.009	-	-
Nerve invasion				
Absence	Ref.	-	-	-
Presence	2.08 (1.28–3.37)	0.003	-	-
Lymph nodes examination				
≤ 15 nodes	Ref.	-	-	-
> 15 nodes	0.83 (0.51–1.34)	0.441	-	-
N stage				
N0	Ref.	-	Ref.	-
N1	2.72 (1.60–4.63)	< 0.001	3.05 (1.68–5.54)	< 0.001
N2	5.19 (2.71–9.94)	< 0.001	6.32 (3.02–13.23)	< 0.001

(*Continued*)

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Table 2 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
T stage				
T1/2	Ref.	-	Ref.	-
T3/4	3.15 (1.75–5.67)	< 0.001	2.32 (1.2–4.48)	0.012
Chemotherapy				
No	Ref.	-	Ref.	-
S-1 based regimen	0.37 (0.20–0.68)	0.001	0.28 (0.14–0.55)	< 0.001
Gemcitabine based regimen	0.37 (0.19–0.75)	0.005	0.27 (0.13–0.56)	< 0.001
Others	0.45 (0.23–0.9)	0.023	0.63 (0.30–1.34)	0.229
CA 19–9 (U/m)				
Normal	Ref.	-	-	-
Elevated	2.41 (1.19–4.89)	0.014	-	-
CEA (ng/mL)				
Normal	Ref.	-	-	-
Elevated	1.56 (0.96–2.53)	0.750	-	-
CGR				
Low value	Ref.	-	-	-
High value	2.06 (1.27–3.33)	0.003	-	-
GNRI				
Low value	Ref.	-	-	-
High value	0.91 (0.57–1.46)	0.690	-	-
PNI				
Low value	Ref.	-	-	-
High value	0.84 (0.53–1.35)	0.480	-	-
CALLY				
Low value	Ref.	-	Ref.	-
High value	0.33 (0.20–0.56)	< 0.001	0.3 (0.17–0.54)	< 0.001
SIRI				
Low value	Ref.	-	-	-
High value	1.63 (1.01–2.62)	0.044	-	-
AISI				
Low value	Ref.	-	-	-
High value	1.72 (1.07–2.79)	0.027	-	-

(*Continued*)

Table 2 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
NLR				
Low value	Ref.	-	-	-
High value	1.55 (0.97–2.48)	0.070	-	-

Abbreviations: CI, confidence interval; Ref, reference; Other abbreviations as in Table 1.

Table 3 Results of Competing Risk Analysis for Ampullary Carcinoma After Pancreaticoduodenectomy

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age				
≤ 65 years	Ref.	-	-	-
> 65 years	0.91 (0.54–1.55)	0.720	-	-
Gender				
Female	Ref.	-	-	-
Male	1.22 (0.71–2.06)	0.460	-	-
Tumor Diameter				
≤ 2 cm	Ref.	-	-	-
2 cm - 5cm	1.3 (0.70–2.42)	0.400	-	-
> 5cm	5.58 (2.05–15.20)	0.001	-	-
Pathological Grade				
Well to moderately	Ref.	-	-	-
Poorly to undifferentiated	2.02 (1.23–3.33)	0.006	-	-
Pathological Type				
Pancreatobiliary	Ref.	-	Ref.	-
Intestinal	0.4 (0.19–0.84)	0.015	0.3 (0.12–0.742)	0.009
Mixed	0.73 (0.26–2.06)	0.560	0.78 (0.2–2.96)	0.710
Others	0.49 (0.19–1.24)	0.130	0.81 (0.28–2.38)	0.700
MVI				
Absence	Ref.	-	-	-
Presence	1.78 (1.08–2.92)	0.023	-	-

(*Continued*)

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Table 3 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Nerve invasion				
Absence	Ref.	-	-	-
Presence	2.04 (1.24–3.38)	0.005	-	-
Lymph nodes examination				
≤ 15 nodes	Ref.	-	-	-
> 15 nodes	0.77 (0.47–1.27)	0.310	-	-
N stage				
N0	Ref.	-	Ref.	-
N1	2.47 (1.42–4.29)	< 0.001	2.23 (1.08–4.59)	0.029
N2	4.88 (2.52–9.46)	< 0.001	4.81 (2.07–11.18)	< 0.001
T stage				
T1/2	Ref.	-	Ref.	-
T3/4	3.49 (1.84–6.59)	< 0.001	2.39 (1.08–5.31)	0.032
Chemotherapy				
No	Ref.	-	Ref.	-
S-1 based regimen	0.42 (0.22–0.80)	0.008	0.42 (0.18–0.98)	0.045
Gemcitabine based regimen	0.42 (0.21–0.85)	0.016	0.37 (0.17–0.83)	0.016
Others	0.4 (0.20–0.84)	0.014	0.83 (0.35–1.95)	0.660
CA 19–9 (U/m)				
Normal	Ref.	-	-	-
Elevated	2.64 (1.21–5.74)	0.015	-	-
CEA (ng/mL)				
Normal	Ref.	-	-	-
Elevated	1.56 (0.94–2.58)	0.085	-	-
CGR				
Low value	Ref.	-	-	-
High value	2.11 (1.29–3.45)	0.003	-	-
GNRI				
Low value	Ref.	-	-	-
High value	0.81 (0.49–1.35)	0.420	-	-

(*Continued*)

Table 3 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
PNI				
Low value	Ref.	-	-	-
High value	0.77 (0.47–1.26)	0.300	-	-
CALLY				
Low value	Ref.	-	Ref.	-
High value	0.31 (0.18–0.52)	< 0.001	0.29 (0.14–0.59)	0.001
SIRI				
Low value	Ref.	-	-	-
High value	1.73 (1.05–2.84)	0.031	-	-
AISI				
Low value	Ref.	-	-	-
High value	1.74 (1.06–2.88)	0.030	-	-
NLR				
Low value	Ref.	-	-	-
High value	1.44 (0.88–2.36)	0.150	-	-

Abbreviations: CI, confidence interval; Ref, reference; Other abbreviations as in Table 1.

PSM Analyses for CALLY Index

Given the significant correlation observed between the CALLY index and patient outcomes, as demonstrated by both multivariate Cox regression and competing risk analyses, we conducted PSM analysis to assess the disparities in its prognostic implications. The values of baseline characteristics between the high CALLY group (n = 100) and the low CALLY group (n = 101) showed significant differences, as detailed in Table 4. Furthermore, according to Kaplan-Meier survival analyses, the 1-, 3-, and 5-year CSS rates for the high CALLY group were 100.0%, 76.6%, and 65.5%, respectively, surpassing those of the low CALLY group, which were 86.3%, 50.2%, and 28.3% (P < 0.001, Figure 1b). Following the PSM process, 132 patients were matched, with 66 in each group. No significant differences were observed in the values of baseline characteristics between the groups (all P > 0.05, Table 4). The 1-, 3-, and 5-year CSS rates in the high CALLY group remained higher than those in the low CALLY group, at 100.0% versus 81.6%, and 74.6% versus 90.23%, 57% versus 36.6%, respectively (P = 0.001, Figure 1c).

Discussion

In this study, in order to comprehensively investigate the factors that may potentially influence patient prognosis, we conducted Cox regression combined with competing risk analysis. The results revealed that key prognostic factors for CSS of AC patients included the pathological type, N stage, T stage, postoperative chemotherapy regimen and the CALLY index. Patients with a high CALLY index value have a better survival outcome. To our knowledge, this is the first study that identified a distinct correlation between the CALLY index and survival outcomes among individuals with AC.

Iida et al first put forward the CALLY index in investigating the prognosis of hepatocellular carcinoma, discovering its remarkable superiority over other conventional indices and its intimate correlation with cancer prognosis.[21] Unlike previous inflammatory and nutritional indicators, this index encompasses C-reactive protein (CRP), albumin, and lymphocyte levels,

Table 4 Pre- Versus Post-PSM Comparison of Baseline Data Stratified by CALLY Index

Variables	Before PSM Process			After PSM Process		
	Low value (n=101,%)	High value (n=100,%)	*P*-value	Low value (n=66,%)	High value (n=66,%)	*P*-value
Age			0.393			0.080
≤ 65 years	46 (45.5)	39 (39.0)		35 (53.0)	24 (36.4)	
> 65 years	55 (54.5)	61 (61.0)		31 (47.0)	42 (63.6)	
Gender			0.244			0.575
Female	33 (32.7)	41 (41.0)		19 (28.8)	23 (34.8)	
Male	68 (67.3)	59 (59.0)		47 (71.2)	43 (65.2)	
Tumor Diameter			0.047			0.873
≤ 2 cm	20 (19.8)	34 (34.0)		16 (24.2)	18 (27.3)	
2 cm - 5cm	74 (73.3)	63 (63.0)		46 (69.7)	45 (68.2)	
> 5cm	7 (6.9)	3 (3.0)		4 (6.1)	3 (4.5)	
Pathological Grade			0.887			1.000
Well to moderately	58 (57.4)	56 (56.0)		40 (60.6)	39 (59.1)	
Poorly to undifferentiated	43 (42.6)	44 (44.0)		26 (39.4)	27 (40.9)	
Pathological Type			0.573			0.586
Pancreatobiliary	63 (62.4)	60 (60.0)		45 (68.2)	39 (59.1)	
Intestinal	22 (21.8)	20 (20.0)		13 (19.7)	14 (21.2)	
Mixed	7 (6.9)	5 (5.0)		2 (3.0)	2 (3.0)	
Others	9 (8.9)	15 (15.0)		6 (9.1)	11 (16.7)	
MVI			0.393			0.593
Absence	55 (54.5)	61 (61.0)		38 (57.6)	42 (63.6)	
Presence	46 (45.5)	39 (39.0)		28 (42.4)	24 (36.4)	
Nerve invasion						1.000
Absence	50 (49.5)	53 (53.0)		35 (53.0)	36 (54.5)	
Presence	51 (50.5)	47 (47.0)	0.673	31 (47.0)	30 (45.5)	
Lymph nodes examination			0.883			1.000
≤ 15 nodes	34 (33.7)	35 (35.0)		20 (30.3)	20 (30.3)	
> 15 nodes	67 (66.3)	65 (65.0)		46 (69.7)	46 (69.7)	
N stage			0.251			0.261
N0	54 (53.5)	65 (65.0)		38 (57.6)	47 (71.2)	
N1	35 (34.7)	26 (26.0)		21 (31.8)	14 (21.2)	
N2	12 (11.9)	9 (9.0)		7 (10.6)	5 (7.6)	
T stage			0.246			0.283

(*Continued*)

Table 4 (Continued).

Variables	Before PSM Process			After PSM Process		
	Low value (n=101,%)	High value (n=100,%)	*P*-value	Low value (n=66,%)	High value (n=66,%)	*P*-value
T1/2	34 (33.7)	42 (42.0)		22 (33.3)	29 (43.9)	
T3/4	67 (66.3)	58 (58.0)		44 (66.7)	37 (56.1)	
Chemotherapy			0.013			0.221
No	44 (43.6)	22 (22.0)		28 (42.4)	19 (28.8)	
S-1 based regimen	28 (27.7)	41 (41.0)		19 (28.8)	28 (42.4)	
Gemcitabine based regimen	13 (12.9)	18 (18.0)		7 (10.6)	10 (15.2)	
Others	16 (15.8)	19 (19.0)		12 (18.2)	9 (13.6)	
CA 19–9 (U/m)			0.008			0.259
Normal	12 (11.9)	27 (27.0)		9 (13.6)	15 (22.7)	
Elevated	89 (88.1)	73 (73.0)		57 (86.4)	51 (77.3)	
CEA (ng/mL)			0.746			0.320
Normal	77 (76.2)	74 (74.0)		52 (78.8)	46 (69.7)	
Elevated	24 (23.8)	26 (26.0)		14 (21.2)	20 (30.3)	
CGR			0.159			0.384
Low value	45 (44.6)	55 (55.0)		29 (43.9)	35 (53.0)	
High value	56 (55.4)	45 (45.0)		37 (56.1)	31 (47.0)	
GNRI			0.002			0.862
Low value	62 (61.4)	39 (39.0)		32 (48.5)	30 (45.5)	
High value	39 (38.6)	61 (61.0)		34 (51.5)	36 (54.5)	
PNI			< 0.001			0.484
Low value	66 (65.3)	34 (34.0)		32 (48.5)	27 (40.9)	
High value	35 (34.7)	66 (66.0)		34 (51.5)	39 (59.1)	
SIRI			<0.001			0.117
Low value	30 (29.7)	71 (71.0)		28 (42.4)	38 (57.6)	
High value	71 (70.3)	29 (29.0)		38 (57.6)	28 (42.4)	
AISI			<0.001			0.081
Low value	31 (30.7)	70 (70.0)		28 (42.4)	39 (59.1)	
High value	70 (69.3)	30 (30.0)		38 (57.6)	27 (40.9)	
NLR			< 0.001			0.163
Low value	32 (31.7)	72 (72.0)		30 (45.5)	39 (59.1)	
High value	69 (68.3)	28 (28.0)		36 (54.5)	27 (40.9)	

Abbreviation: PSM, propensity score matching analysis; Other abbreviations as in Table 1.

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providing a more comprehensive reflection of patients' inflammatory status, nutritional status, and immune status. Later, the CALLY index has shown its value in predicting the prognosis of a variety of malignant tumors.[17–20] Yang et al's study found the CALLY index to be a superior independent prognostic marker for colorectal cancer, outperforming traditional factors like NLR, PLR, SII, and mGPS.[22] Moreover, analogous findings have been reported in cases of esophageal and gastric cancers.[23,24] The research by Shinnosuke et al further corroborated these findings, indicating that a lower CALLY index is significantly correlated with diminished OS and RFS.[25] Collectively, these studies highlight the significant role of the CALLY index in prognostic prediction.

Our results revealed that an elevated CALLY index (representing lower CRP, higher serum albumin and higher lymphocyte level) was associated with a better survival outcome for patients with AC. As known, CRP is the most commonly used inflammatory biomarker in clinic.[26] The chronic inflammatory environments facilitate the proliferation and invasion of cancer cells, as inflammatory mediators such as cytokines and chemokines can stimulate signaling pathways in tumor cells, thereby accelerating tumor progression.[27] Additionally, inflammation may also induce DNA damage and genetic mutations through the generation of reactive oxygen and nitrogen species, increasing the risk of tumorigenesis.[28] Nutritional status emerges as another crucial factor influencing tumor development. Albumin, the primary protein synthesized by the liver, is widely used to evaluate the nutritional status of patients. The consumption of malignancy, diminished hepatic synthetic function, and disorders of digestion and absorption can all lead to a decline in albumin levels in patients, thereby worsening their nutritional status.[29] Malnutrition impairs the immune system, diminishing its surveillance and elimination capabilities against tumor cells, thereby accelerating tumor growth. Moreover, the normalcy of lymphocyte proportion directly mirrors the state of human immune function. A decrease in lymphocyte proportion often indicates immune suppression, whereas an increase may signify an active immune response to a particular stimulus. Previous studies have shown lymphocyte can infiltrate into the tumor microenvironment, disrupting the growth and dissemination capabilities of tumor cells, thereby establishing an effective defense against them.[30,31]

Except for the CALLY index, we found that N stage, T stage, pathological type, and postoperative chemotherapy regimen were statistically prognostic variables for AC with PD. In our study, the results showed that individuals with tumors classified at T3/4 stages experienced a less favorable prognosis in contrast to those with T1/2 stage. Similarly, patients with N1/2 stage lymph node involvement had a poorer prognosis compared to those with N0 stage. The AJCC TNM system serves as the most commonly used standard for assessing the prognosis of AC patients. A higher T stage also indicates larger tumor size, more extensive invasion, higher risk of distant metastasis, and poorer prognosis. Previous studies have demonstrated that tumor size and depth of invasion are significant factors influencing the prognosis of patients with AC.[32–34] Lymph node metastasis is also a significant factor affecting the prognosis of patients with AC, and numerous previous research have consistently demonstrated that patients with lymph node metastasis have a lower survival rate.[35–37] A study involving 1301 patients demonstrated that patients with negative lymph nodes had significantly higher disease-specific survival rates at both 5 and 10 years than those with positive lymph nodes.[38] Additionally, studies have shown that the risk of lymph node metastasis indeed increases with higher T stages, resulting in a poorer prognosis.[39,40] Based on the original site, AC can be histologically categorized into intestinal, pancreatobiliary and mixed types.[41] Each subtype of AC appears to exhibit biological behavior and prognosis akin to those of periampullary carcinomas. Notably, the pancreatobiliary subtype is associated with a higher incidence of lymph node involvement and a less favorable survival rate when contrasted with the intestinal subtype.[42,43] Similar to their research, our results also indicated that intestinal type AC exhibits more favorable outcomes compared to pancreaticobiliary type AC, while the mixed-type and other rare subtypes showed no significant difference. Regarding postoperative chemotherapy, our results indicated that patients who received an S-1 based regimen or Gemcitabine based regimen experienced improved survival rates as opposed to those who forewent chemotherapy. The efficacy of postoperative chemotherapy for ampullary cancer remains controversial. Some research has implied that adjuvant chemotherapy could enhance survival rates among individuals with AC, particularly for those exhibiting more advanced T- and N-stage conditions.[44,45] However, there are some studies that hold different opinions, their study indicated that postoperative chemotherapy had no impact on reducing recurrence or improving survival outcomes.[46,47] In addition, Kang et al conducted a retrospective analysis of 475 patients, revealing that postoperative chemotherapy did not confer a significant benefit in terms of OS or DFS.[48] However, since these studies were retrospective in nature, further research is needed to better understand the role of postoperative chemotherapy in cancer treatment.

This study is constrained by several limitations. First, it was a single-center study with a limited sample size of enrolled patients. Secondly, being retrospective in nature, it may be susceptible to selection bias. Thirdly, due to the limited sample size, several rare pathological subtypes have been grouped together as "others". However, it is recognized that their prognoses may differ. Moreover, the research utilizing AI algorithms to predict the prognosis of cancer patients has been increasingly abundant in recent years,[49] meriting further exploration in our future studies.

Conclusion

In conclusion, the CALLY index, in conjunction with N stage, T stage, pathological subtype, and postoperative chemotherapy, emerges as an independent predictor of survival outcomes in individuals with AC. For patients with a lower CALLY index, it is crucial that physicians provide heightened attention, including thorough postoperative surveillance and appropriate chemotherapy, to optimize prognostic outcomes. Further high-quality research is warranted to substantiate the influence of these factors in future studies.

Data Sharing Statement

Data can be provided by the corresponding author upon reasonable request.

Ethical Approval Statement

This retrospective analysis was conducted in accordance with the ethical principles of the Helsinki Declaration, obtained ethical approval from the Sun Yat-sen University Cancer Center Ethics Committee (Approval No. C2021-003-X02), and was granted a waiver for informed consent in view of its retrospective nature. Furthermore, patient confidentiality was rigorously maintained through the anonymization of all data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest associated with this study.

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