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ORIGINAL ARTICLE

Identifying occult high-risk features and stratified management strategies following curative resection for ampullary adenocarcinoma

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ABSTRACT

Objective: The aim of the current study was to identify independent prognostic factors, evaluate differential adjuvant chemotherapy efficacy across clinicopathologic subgroups, and define adjuvant chemotherapy-sensitive populations.

Methods: A retrospective analysis of 168 AAC patients undergoing curative pancreaticoduodenectomy (2011–2020) was performed. Cases were classified into intestinal (28.0%), pancreatobiliary (30.4%), and mixed subtypes (18.5%) per NCCN (v2.2025) criteria. Independent prognostic factors for AAC patients were identified through uni- and multi-variable Cox proportional hazards modeling and subgroup analyses were stratified by age range, gender, differentiation, T stage, N stage, BVI, TDs, and PNI.

Results: The pancreatobiliary signature (HR = 2.884, $P < 0.001$) and BVI (HR = 2.330, $P = 0.001$) were independent poor prognostic factors. Adjuvant chemotherapy improved overall survival (OS) in the following AAC patients: T3–T4 stage (HR = 0.485, $P = 0.050$); N1–N2 stage (HR = 0.365, $P = 0.008$); and TD-positive (HR = 0.401, $P = 0.026$). The median OS increased from 22.3–51.3 months with adjuvant chemotherapy in TD-positive patients ($P = 0.019$). TD positivity conferred a worse prognosis in BVI-negative subgroups (OS: HR = 3.840, 95% CI: 2.058–7.166, $P < 0.001$; and progression-free survival (PFS): HR = 2.950, 95% CI: 1.550–5.617, $P = 0.002$).

Conclusions: The pancreatobiliary signature and BVI constitute critical high-risk pathologic features in AAC. TD status identified high-risk cohorts, thus enabling postoperative risk-stratified treatment strategies. In patients negative for pancreatobiliary signature or BVI, TD positivity predicted significantly worse survival.

KEYWORDS Adjuvant chemotherapy; ampullary adenocarcinoma; pancreaticoduodenectomy; prognostic factors; tumor deposits; vascular invasion

Introduction

Ampullary adenocarcinoma (AAC) is a rare gastrointestinal malignancy that accounts for < 1% of all gastrointestinal tumors[1]. The clinical management of AAC poses distinct challenges given the unique anatomic location and marked biological heterogeneity[2]. Curative pancreaticoduodenectomy remains the only potentially curative treatment for AAC but the postoperative recurrence rates remain high (30%–50%) with 5-year overall survival (OS) rates ranging between 40% and 60%[3]. Although recent advances have deepened the understanding of the molecular features and histopathologic subtypes (intestinal and pancreatobiliary) of AAC, robust evidence supporting prognostic stratification and postoperative adjuvant therapy strategies are limited[4]. It was not until 2022 that the first National Comprehensive Cancer Network (NCCN) guidelines incorporated AAC-specific recommendations[5]. Nevertheless, the indications and efficacy of adjuvant chemotherapy for AAC continue to be debated.

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Previous studies suggested that the histopathologic subtypes of AAC have a substantial influence on prognosis[6]. Intestinal (*CDX2+/MUC1−*) and pancreatobiliary adenocarcinoma (*CDX2−/MUC1+*) exhibit distinct genomic profiles, invasiveness, and survival outcomes. However, the differential sensitivity of AAC to adjuvant therapy remains unclear. In addition, although pathologic features, such as blood vessel invasion (BVI), tumor deposits (TDs), and perineural invasion (PNI), have been established as poor prognostic factors in other gastrointestinal cancers[7-10], the prognostic importance in AAC remains to be validated.

This single-center, large-sample retrospective study aimed to address three critical questions: (1) the independent prognostic impact of histopathologic subtypes and classic pathological parameters; (2) the differential efficacy of adjuvant chemotherapy across clinicopathologic subgroups; and (3) the identification of potential populations benefiting from adjuvant chemotherapy. An analysis of long-term follow-up data from 168 patients undergoing curative pancreaticoduodenectomy combined with multivariate Cox regression and subgroup stratification was performed, which identified TD as a potential predictive marker for postoperative risk-stratified treatment in AAC and established the pancreatobiliary signature and BVI as core independent prognostic factors. These findings provide critical evidence for optimizing risk-stratified postoperative management and lay a foundation for future prospective studies.

Methods

Patient selection

All adult patients who underwent pancreatoduodenectomy for AAC at Tianjin Medical University Cancer Institute & Hospital (January 1, 2011–December 31, 2020) were included in this study and the pathologic findings were confirmed. Patients who underwent palliative procedures or with an R2 resection or distant metastases were not included. A total of 168 patients were included in this retrospective analysis. This study was apprvoed by the Ethics Committee of Tianjin Medical University Cancer Institute & Hospital (Approval No. E20230697).

Patient treatment and survival data

All patients underwent a standardized pancreaticoduodenectomy followed by adjuvant chemotherapy with gemcitabine- or fluorouracil-based regimens for at least one cycle. OS was measured from the date of surgery until death from any cause or last follow-up evaluation. Progression-free survival (PFS) was evaluated according to RECIST 1.1 criteria and defined as the time from surgery to radiographically confirmed disease progression or death from any cause. BVI, TDs, and PNI were documented in accordance with the pathologic report.

Histopathologic subtypes

Intestinal and pancreatobiliary subtypes were classified based on cytologic and architectural features and immunochemistry marker staining in accordance with the NCCN guidelines [v2 (2025) for AAC]. *CDX2* and *MUC1* were considered the major biomarkers to distinguish the two subtypes (pancreatobiliary subtype: *CDX2* negative, *MUC1* positive; and intestinal subtype: *CDX2* positive, *MUC1* negative). The other biomarkers in making this distinction were *MUC2*, *CK20*, and *CK7*. Cases exhibiting heterogeneous marker positivity and ambiguous cytologic features were classified as the mixed subtype. All pathologic evaluations were independently reviewed and confirmed by two senior pathologists using a double-blinded method.

Statistical analysis

Normally distributed variables were reported as the mean ± standard deviation. Categorical variables are presented as frequencies and proportions. Categorical data were compared using the chi square-test, whereas numerical data were compared by using the Student's *t*-test for normally distributed data and non-normally distributed data with the non-parametric equivalent using the Mann–Whitney *U* test. Patients who died within 30 d after surgery were excluded from survival analysis. Kaplan-Meier curves were generated to visualize survival outcomes with between-group differences assessed by the log-rank test. Uni- and multi-variable Cox proportional hazards models were used to evaluate prognostic factors, including age range, gender, histopathologic subtype, differentiation, adjuvant chemotherapy, T stage, N stage, BVI, TD, and PNI. All interaction *P* values were adjusted using the Benjamini-Hochberg method [false discovery rate (FDR) = 0.05]. Data were analyzed using SPSS 29.0 software (Chicago, IL, USA).

Results

Patient demographics and tumor characteristics

A total of 168 patients with AAC who underwent curative-intent surgery were included in this study. Data were accrued between January 1, 2011 and December 31, 2020 from patients with pathologically confirmed peri-AAC at Tianjin Medical University Cancer Institute & Hospital.

The median patient age was 61.1 years. Ninety-five patients (56.5%) were male and 73 (43.5%) were female. Forty-seven patients (28.0%) had an intestinal subtype, 51 (30.4%) had a pancreatobiliary subtype, and 31 (18.5%) had mixed intestinal and pancreatobiliary variants based on the final pathologic examination (**Figure 1**). The remaining 39 patients were the unclassified subtype due to failure to meet definitive subtyping criteria (e.g., ambiguous features below the mixed-type threshold and atypical/negative marker expression). Eighty-five patients (50.6%) had a T3–T4 stage tumor and 64 (38.1%) had lymph node invasion based on the final pathologic results. Adverse prognostic features, such as poor differentiation [79 (47.0%)], BVI [48 (28.6%)], TD [54 (32.1%)], and PNI [36 (21.4%)] were frequently observed. A total of 102 patients (60.7%) underwent adjuvant chemotherapy, whereas 66 (39.3%) had surgery only (**Table 1**).

Entire cohort survival analysis

The cohort (n = 168) had a median follow-up of 160 months with a median OS of 57 months and a median PFS of 26 months. Censoring included 12 patients who were lost to follow-up, 2 had untraceable external hospital data, and 28 were alive at the end of the follow-up period. Kaplan-Meier analysis demonstrated a significantly shorter OS in the following patients: poor differentiation (44 *vs*. 64 *vs*. 110 months; $P < 0.001$); advanced N-stage (N2:24 *vs*. N1:36 *vs*. N0:116 months; $P < 0.001$); pancreatobiliary subtype (43 *vs*. 80 months; $P < 0.001$); BVI-positive (23 *vs*. 116 months; $P < 0.001$); TD-positive (36 *vs*. 115 months; $P < 0.001$); and PNI-positive (27 *vs*. 81 months; $P < 0.001$; **Figure 2**). A PFS analysis showed consistent results (**Figure S1**). Representative imaging follow-up revealed hepatic metastasis within 8 months postoperatively (PFS = 7.9 months) in a patient with the pancreatobiliary subtype versus metastasis at 31.7 months (PFS = 31.7 months) in a patient with an intestinal subtype (**Figure 3**).

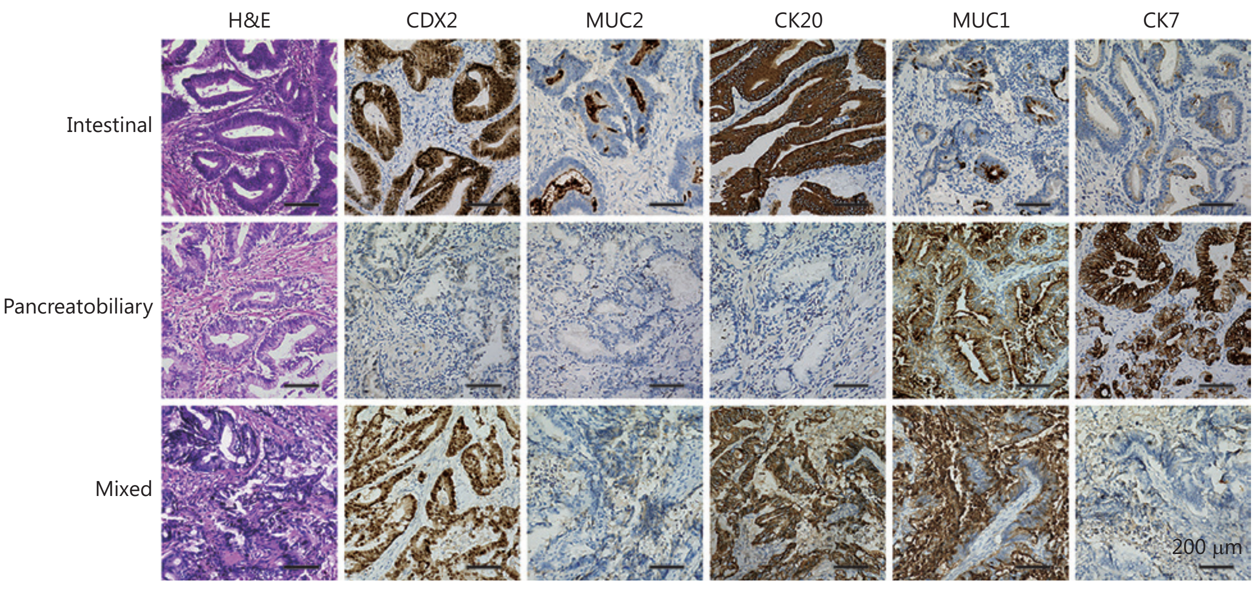

Figure 1 Representative histopathologic staining of AAC subtypes. Intestinal subtype (glandular architecture: CDX2+, MUC2+/−, CK20+, MUC1+/−, CK7−); Pancreatobiliary subtype (monolayered cuboidal cells: CDX2−, MUC2−, CK20−, MUC1+, CK7+); Mixed subtype (co-expression: CDX2+, MUC2+/−, CK20+, MUC1+, CK7−). Scale bars: 200 μm.

Table 1 Demographic and clinicopathologic characteristics of the overall cohort

Characteristics	Patients, *n* (%)
	(*n* = 168)
Age range, years	
< 65	107 (63.7)
65–80	61 (36.3)
Sex	
Male	95 (56.5)
Female	73 (43.5)
Differentiation	
Well	24 (14.3)
Moderate	65 (38.7)
Poor	79 (47.0)
T stage	
T1-T2	83 (49.4)
T3-T4	85 (50.6)
N stage	
N0	104 (61.9)
N1	41 (24.4)
N2	23 (13.7)
Pathologic stage	
I	52 (31.0)
II	49 (29.2)
III	67 (39.9)
Histologic subtype	
Intestinal	47 (28.0)
Pancreatobiliary	51 (30.4)
Mixed	31 (18.5)
Unclassified	39 (23.2)
CDX2	
Yes	74 (44.1)
No	94 (55.9)
MUC2	
Yes	45 (26.8)
No	123 (73.2)
CK20	
Yes	77 (45.8)
No	91 (54.2)
MUC1	
Yes	78 (46.4)
No	90 (53.6)
CK7	
Yes	93 (55.4)
No	75 (44.6)
BVI	
Yes	48 (28.6)
No	120 (71.4)
TD	
Yes	54 (32.1)
No	114 (67.9)
PNI	
Yes	36 (21.4)
No	132 (78.6)
Adjuvant chemotherapy	
Yes	102 (60.7)
No	66 (39.3)

Patients undergoing curative pancreaticoduodenectomy for AAC (*n* = 168). Unclassified group included cases with atypical IHC expression. TD: Tumor deposits are defined as extranodal tumor cell clusters (> 10 cells) ≥ 3 mm from the primary tumor. BVI, blood vessel invasion; PNI, perineural invasion.

Delineating the pancreatobiliary signature based on biomarkers

Multicollinearity analysis revealed significant collinearity in the original pancreatobiliary subtype variables (**Table S1**). Immunohistochemical validation demonstrated that the pancreatobiliary subtype was strongly associated with a *CDX2−/MUC2−/MUC1+/CK7+* expression profile (**Figure S2**). Accordingly, a composite variable (pancreatobiliary signature, defined as *CDX2−/MUC2−/MUC1+/CK7+*) was constructed

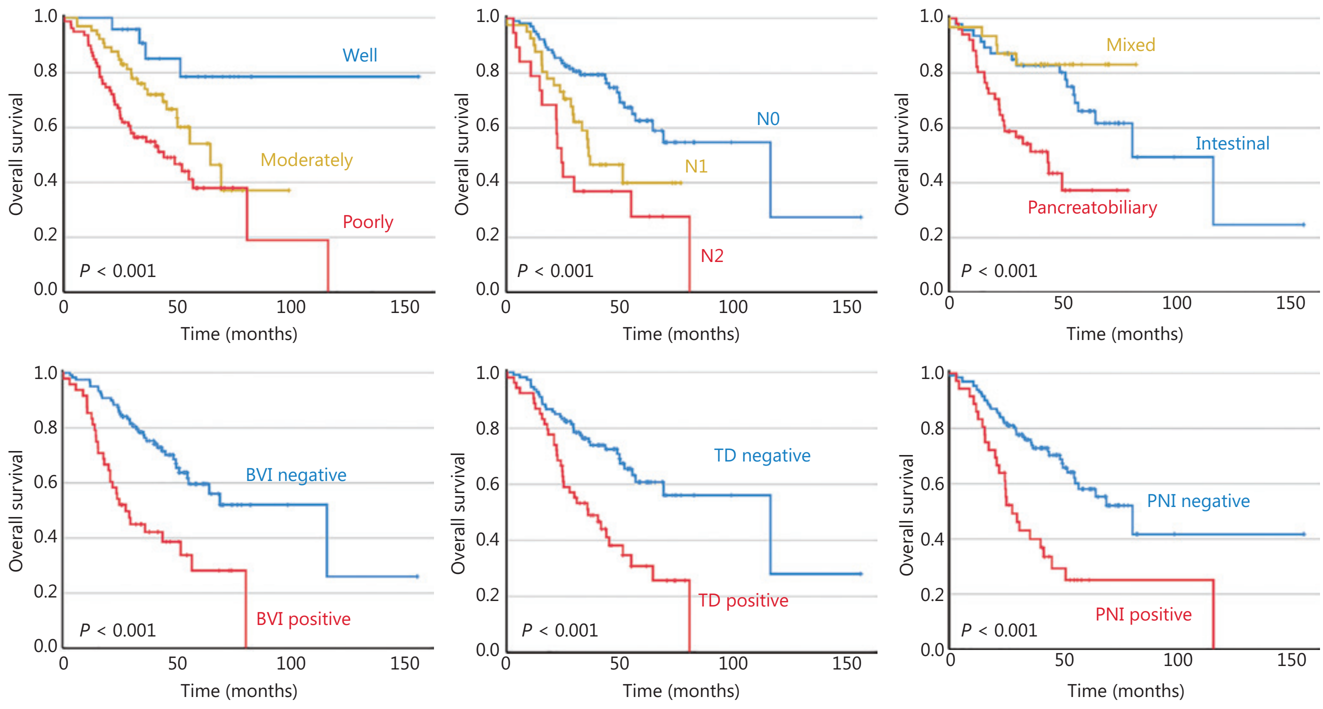

Figure 2 Kaplan-Meier curves for overall survival prognostic factors in the overall cohort. Differentiation (poor *vs.* well *vs.* moderate; $P < 0.001$); N stage (N2 *vs.* N1 *vs.* N0; $P < 0.001$); Histologic subtype (pancreatobiliary *vs.* intestinal *vs.* mixed; $P < 0.001$); BVI status (positive *vs.* negative; $P < 0.001$); TD status (positive *vs.* negative; $P < 0.001$); PNI status (positive *vs.* negative; $P < 0.001$). *P* values by log-rank test.

that effectively resolved the collinearity issue (all post-substitution $VIF < 5$).

Multivariate analysis identifies independent prognostic factors in AAC

Multivariate Cox regression analysis identified differentiation (HR = 1.682, 95% CI 1.012–2.797; $P = 0.045$), N stage (HR = 1.969, 95% CI 1.194–3.247; $P = 0.008$), pancreatobiliary signature (HR = 2.884, 95% CI 1.725–4.281; $P < 0.001$), *CK20* (HR = 0.577, 95% CI 0.348–0.958; $P = 0.033$), BVI (HR = 2.330, 95% CI 1.398–3.883; $P = 0.001$), and PNI (HR = 2.417, 95% CI 1.372–4.258; $P = 0.002$) as independent prognostic factors for OS in AAC (**Table 2**). Additionally, differentiation (HR = 1.917, 95% CI 1.120–3.280; $P = 0.018$), pancreatobiliary signature (HR = 1.820, 95% CI 1.042–3.178; $P = 0.035$), and lack of adjuvant chemotherapy (HR = 2.007, 95% CI 1.108–3.633; $P = 0.021$) were independent predictors of PFS (**Table 3**). Notably, adjuvant chemotherapy did not significantly improve OS in the overall cohort without stratification (**Table 2**).

Subgroup-specific survival benefit of adjuvant chemotherapy

The heterogeneity of adjuvant chemotherapy efficacy significantly improved outcomes in high-risk subgroups, as follows: T3–T4 stage (HR = 0.485, 95% CI 0.258–0.911; $P = 0.050$); N1–N2 stage (HR = 0.365, 95% CI 0.185–0.721; $P = 0.008$); and TD positivity (HR = 0.401, 95% CI 0.195–0.822; $P = 0.026$). Forest plot analysis showed adjuvant chemotherapy reduced mortality risk by 60% in TD-positive patients (**Figure 4**). Survival curves confirmed a significantly prolonged median OS with adjuvant chemotherapy for T3–T4 stage (64.6 *vs.* 32.6 months; $P = 0.043$), N1–N2 stage (41.7 *vs.* 22.2 months; $P = 0.005$), and TD positivity (51.3 *vs.* 22.3 months; $P = 0.019$; **Figure 5**). No significant PFS benefit was detected in any subgroup. Notably, multivariate analysis showed that TD was not an independent prognostic factor for OS or PFS in chemotherapy-treated patients (**Tables S2 and S3**), suggesting that prognostic improvement may be context-dependent.

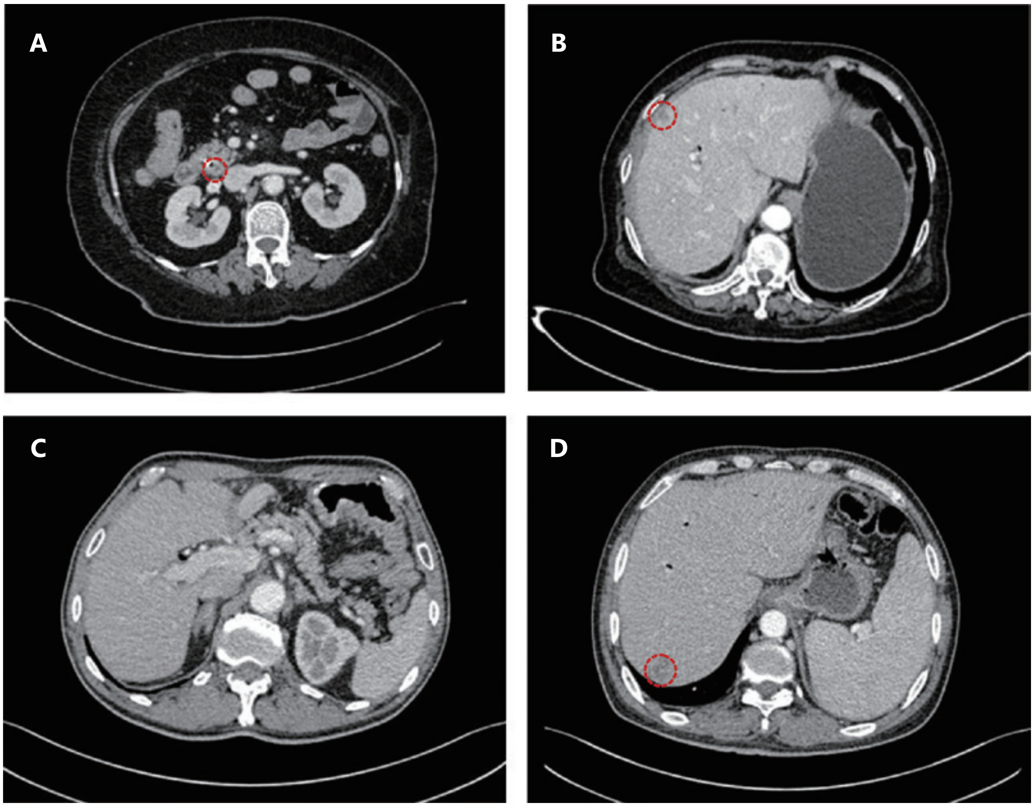

Figure 3 Imaging progression patterns by histologic subtype. Pancreatobiliary subtype: (A) Primary tumor (red circle); (B) Liver metastasis (red circle) detected 7.9 months postoperatively. Intestinal subtype: (C) No progression at 10 months; (D) New liver metastases (red circle) at 31.7 months. Significant PFS difference (P < 0.001).

Table 2 Uni- and multi-variable Cox regression for overall survival in the overall cohort

	Univariable		Multivariable	
	Hazard ratio [95% CI]	BH_adjusted_*P*	Hazard ratio [95% CI]	*P* value
Age range	1.284 [0.795–2.075]	0.307		
Sex	1.422 [0.895–2.258]	0.166		
Differentiation	2.257 [1.404–3.629]	**0.001**	1.682 [1.012–2.797]	**0.045**
T stage	1.552 [0.967–2.493]	0.095	0.786 [0.463–1.333]	0.371
N stage	2.744 [1.711–4.402]	**< 0.001**	1.969 [1.194–3.247]	**0.008**
Pancreatobiliary signature	2.995 [1.829–4.901]	**< 0.001**	2.884 [1.725–4.821]	**< 0.001**
CK20	0.566 [0.349–0.919]	**0.036**	0.577 [0.348–0.958]	**0.033**
Adjuvant chemotherapy	0.720 [0.447–1.160]	0.195		
BVI	2.855 [1.781–4.575]	**< 0.001**	2.330 [1.398–3.883]	**0.001**
TD	2.557 [1.602–4.080]	**< 0.001**	1.249 [0.739–2.111]	0.406
PNI	2.804 [1.723–4.562]	**< 0.001**	2.417 [1.372–4.258]	**0.002**

Covariates: age range; gender; differentiation; T stage; N stage; adjuvant; chemotherapy; CK20; BVI; TD; and PNI. Pancreatobiliary signature defined as CDX2−/MUC2−/MUC1+/CK7+ (resolving multicollinearity). In univariate analysis, differentiation, N stage, pancreatobiliary signature, CK20, BVI, TD and PNI showed significant associations with OS. Multivariate analysis confirmed independent prognostic factors. P < 0.05.

Table 3 Uni- and multi-variable Cox regression for progression-free survival in the overall cohort

	Univariable		Multivariable	
	Hazard ratio [95% CI]	BH_adjusted_*P*	Hazard ratio [95% CI]	*P* value
Age range	0.697 [0.403–1.204]	0.269		
Sex	1.047 [0.639–1.716]	0.855		
Differentiation	2.211 [1.341–3.648]	**0.021**	1.917 [1.120–3.280]	**0.018**
T stage	1.205 [0.734–1.979]	0.562	0.696 [0.399–1.215]	0.203
N stage	2.170 [1.319–3.570]	**0.013**	1.653 [0.975–2.803]	0.062
Pancreatobiliary signature	1.971 [1.144–3.398]	**0.027**	1.820 [1.042–3.178]	**0.035**
CK20	0.867 [0.528–1.421]	0.628		
Adjuvant chemotherapy	2.115 [1.183–3.779]	**0.025**	2.007 [1.108–3.633]	**0.021**
BVI	2.169 [1.304–3.607]	**0.011**	1.367 [0.793–2.357]	0.260
TD	2.002 [1.213–3.304]	**0.018**	1.378 [0.795–2.388]	0.254
PNI	1.843 [1.065–3.190]	**0.045**	1.568 [0.841–2.922]	0.157

Lack of adjuvant chemotherapy significantly increases progression risk (HR = 2.007, P = 0.021). In univariate analysis, differentiation, N stage, pancreatobiliary signature, adjuvant chemotherapy, BVI, TD and PNI showed significant associations with PFS. Multivariate analysis confirmed differentiation, pancreatobiliary signature and adjuvant chemotherapy as independent prognostic factors. P < 0.05.

Variable	**Hazard ratio [95% CI]**	***P* value**
Age range		
<65	0.588 [0.317–1.091]	0.186
65–80	1.020 [0.477–2.183]	0.959
Sex		
Male	0.733 [0.377–1.423]	0.358
Female	0.637 [0.316–1.283]	0.414
Differentiation		
Well and moderate	0.911 [0.425–1.954]	0.811
Poor	0.509 [0.274–0.946]	0.066
T stage		
T1–T2	1.120 [0.520–2.412]	0.771
T3–T4	**0.485 [0.258–0.911]**	**0.050**
N stage		
N0	0.882 [0.433–1.795]	0.728
N1–N2	**0.365 [0.185–0.721]**	**0.008**
Pancreatobiliary signature		
Negative	1.049 [0.555–1.980]	0.883
Positive	0.467 [0.212–1.028]	0.118
CK20		
Negative	0.738 [0.406–1.342]	0.640
Positive	0.797 [0.356–1.784]	0.581
BVI		
Negative	0.616 [0.329–1.151]	0.128
Positive	0.539 [0.247–1.175]	0.240
TD		
Negative	0.978 [0.494–1.934]	0.948
Positive	**0.401 [0.195–0.822]**	**0.026**
PNI		
Negative	0.844 [0.461–1.544]	0.844
Positive	0.508 [0.230–1.121]	0.186

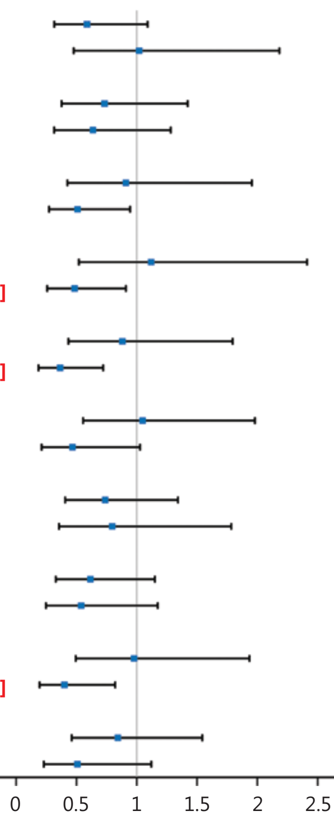

Figure 4 Forest plot for adjuvant chemotherapy benefit in high-risk subgroups. Adjuvant chemotherapy significantly improved OS in the following AAC patient subgroups: T3–T4 stage (HR = 0.485); N1–N2 stage (HR = 0.365); and TD-positive (HR = 0.401; all P < 0.05). There was a 60% mortality reduction in the TD-positive subgroup.

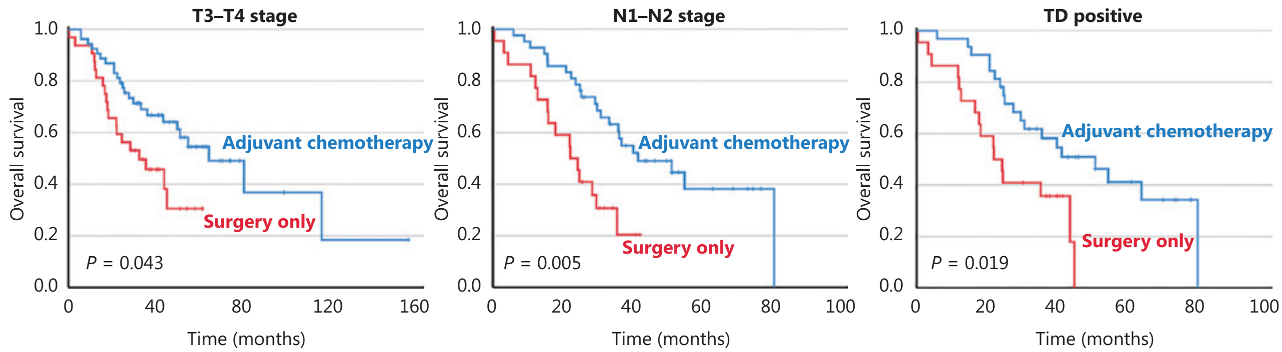

Figure 5 Survival curves demonstrating adjuvant chemotherapy benefit in the following AAC high-risk subgroups: T3–T4 stage, 64.6 *vs.* 32.6 months (P = 0.043); N1–N2 stage, 41.7 *vs.* 22.2 months (P = 0.005); and TD-positive, 51.3 *vs.* 22.3 months (P = 0.019).

Variable	Hazard ratio [95% CI]	*P* value
Differentiation	1.425 [0.547–3.712]	0.819
Well and moderate	2.734 [1.291–5.789]	0.018
Poor	1.959 [1.072–3.578]	0.029
T stage	0.632 [0.236–1.691]	0.840
T1–T2	3.328 [1.529–7.245]	0.004
T3–T4	1.996 [1.075–3.706]	0.029
N stage	0.958 [0.360–2.549]	0.932
N0	2.704 [0.998–4.311]	0.051
N1–N2	1.942 [1.013–3.723]	0.092
Pancreatobiliary signature	0.587 [0.223–1.548]	0.987
Negative	2.842 [1.580–5.113]	0.001
Positive	1.684 [0.779–3.638]	0.185
CK20	1.178 [0.451–3.076]	0.867
Negative	2.302 [1.270–4.172]	0.012
Positive	2.613 [1.218–5.608]	0.014
BVI	**0.255 [0.098–0.661]**	**0.035**
Negative	**3.840 [2.058–7.166]**	**<0.001**
Positive	0.934 [0.453–1.925]	0.853
PNI	0.817 [0.276–2.416]	1.000
Negative	2.071 [1.128–3.805]	0.038
Positive	1.567 [0.619–3.967]	0.343

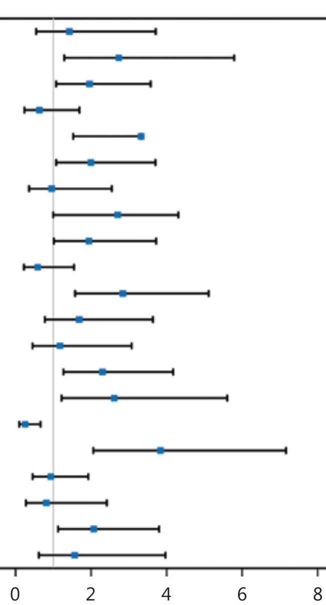

Figure 6 Interaction effects of TD and BVI on overall survival. Antagonistic interaction between TD and BVI (β = −1.366, P = 0.035). TD positivity significantly worsened OS in BVI-negative patients (HR = 3.840, P < 0.001).

Interaction effects and context-dependent prognostic value of TD

An interaction analysis between TD and adjuvant chemotherapy revealed that chemotherapy did not significantly modify the prognostic risk associated with TD (interaction HR = 0.46, β = −0.769, 95% CI: 0.178–1.208; P = 0.115; **Table S4**). Therefore, whether the impact of TD on prognosis in the overall cohort was dependent on other clinicopathologic factors was determined. Interaction analysis demonstrated a significant antagonistic interaction between TD and BVI for OS (β = −1.366; P = 0.035) and PFS (β = −1.422; P = 0.049). TD positivity conferred markedly worse prognosis in BVI-negative patients (OS: HR = 3.840, 95% CI: 2.058–7.166; P < 0.001; PFS: HR = 2.950, 95% CI: 1.550–5.617; P = 0.002; **Figures 6 and 7**). Furthermore, TD had a significant interaction with the pancreatobiliary signature for PFS (β = −1.525; P = 0.049) and increased progression risk in pancreatobiliary signature-negative patients (HR = 2.903, 95% CI: 1.604–5.255; P = 0.001; **Figure 7**). Survival analysis validated these context-dependent

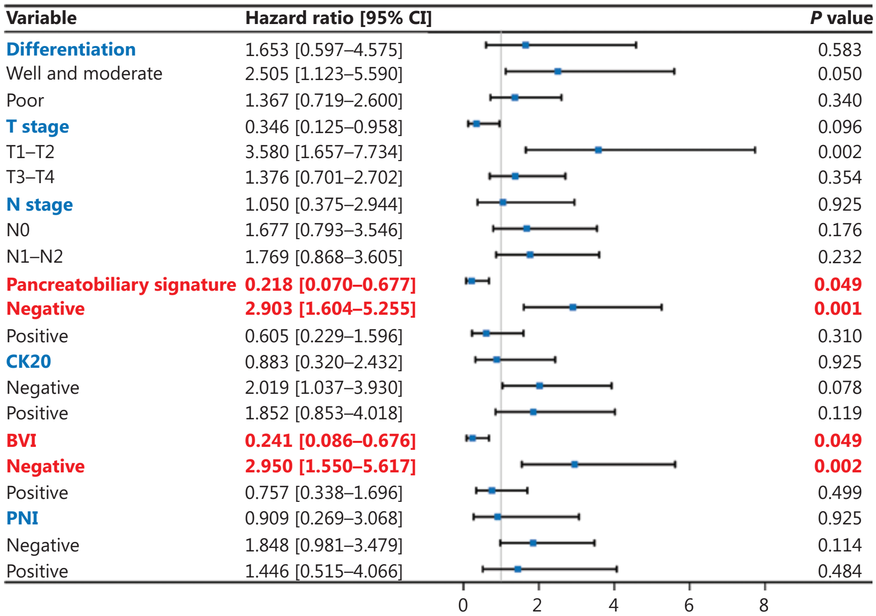

Figure 7 Interaction effects of TD on progression-free survival. TD-BVI interaction ($\beta = -1.422$, $P = 0.049$); TD predicted poor PFS in the BVI-negative group (HR = 2.950, $P = 0.002$). TD-pancreatobiliary signature interaction ($\beta = -1.525$, $P = 0.049$); TD increased progression risk in the pancreatobiliary signature-negative group (HR = 2.903, $P = 0.001$).

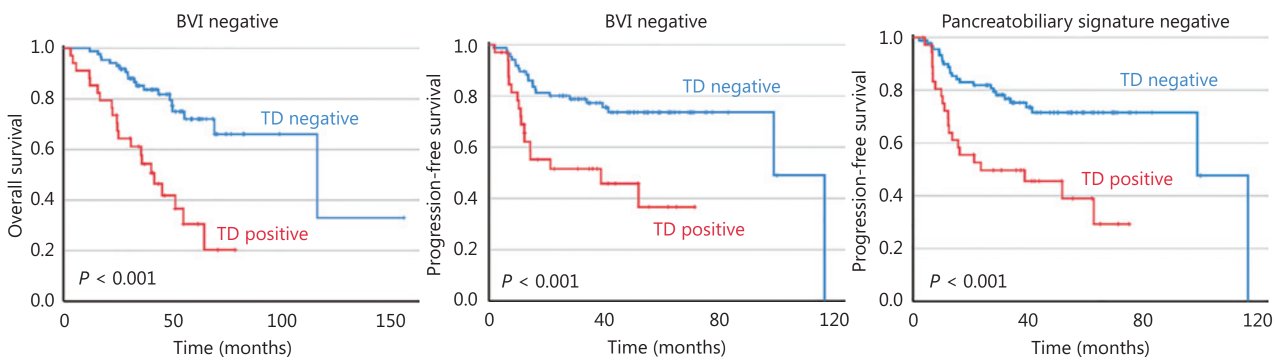

Figure 8 Context-dependent survival impact of TD in key subgroups. TD positivity significantly reduced OS in BVI-negative patients (38.7 *vs.* 96.4 months; $P < 0.001$); TD positivity shortened PFS in BVI-negative patients (22.6 *vs.* 89.0 months; $P < 0.001$); TD positivity worsened PFS in pancreatobiliary signature-negative patients (23.4 *vs.* 91.2 months; $P < 0.001$).

effects. Specifically, BVI-negative, TD-positive patients had a substantially reduced median OS (38.7 *vs.* 96.4 months; $P < 0.001$) and PFS (22.6 *vs.* 89.0 months; $P < 0.001$), while pancreatobiliary signature-negative, TD-positive patients had a shortened median PFS (23.4 *vs.* 91.2 months; $P < 0.001$; **Figure 8**).

Discussion

AAC is a rare malignant tumor that lacks sufficient evidence supporting optimal treatment options and guidelines[11]. The first version of the NCCN guidelines of ampullary carcinoma did not appear until 2022. A radical pancreatoduodenectomy is the standard surgical approach for ampullary carcinoma[12-14]. However, no randomized controlled trial has provided evidence on whether ampullary carcinoma should be administered after a radical resection. To date, several randomized clinical trials and retrospective studies have been conducted for adjuvant chemotherapy in patients with resected periampullary carcinoma[15,16]. The ESPAC-3 trial is a prospective multicenter randomized phase III trial involving 428 patients with AAC who underwent periampullary cancers and received adjuvant chemotherapy versus observation. No significant survival benefit was ascribed to the chemotherapy regimen group and subgroup analysis of the potential benefit in AAC patients was not reported[17,18]. In a retrospective study Shin and colleagues reported that adjuvant therapy was associated with improved disease-free and OS in advanced stage AAC but not for early-stage disease of adjuvant chemotherapy in resected AAC[19]. In contrast, a retrospective study conducted in the Republic of Korea showed that AAC was not associated with survival benefits, even in advanced stages[20].

The current study used multivariate Cox proportional hazards regression analysis to confirm that the pancreatobiliary signature (HR = 2.134, 95% CI 1.038–4.387; P = 0.039) and BVI (HR = 2.290, 95% CI 1.209–4.335; P = 0.011) serve as independent prognostic risk factors for AAC and among patients receiving postoperative adjuvant chemotherapy (pancreatobiliary signature: HR = 2.134, 95% CI 1.038–4.387; P = 0.039; BVI: HR = 2.290, 95% CI 1.209–4.335; P = 0.011). Stratified analysis revealed significant survival advantages in the following high-risk populations receiving adjuvant chemotherapy: locally advanced tumors (T3–T4 stage); node-positive metastases (N1–N2 stage); and TD positivity.

TDs are defined as the irregular aggregation of discrete tumor cells in soft tissues or fats that are discontinuous with the primary lesion[21]. TDs show no evidence of residual lymph node architecture but are within the lymphatic drainage of the primary cancer[22-24]. TDs have been confirmed to have an adverse impact on the prognosis of colorectal cancer and pancreatic cancer[24-26] but there are no reports on ampullary carcinoma. In the current study TD was not an independent risk factor for patients with AAC patients. However, TD-positive patients exhibited a 60% reduction in mortality risk following adjuvant chemotherapy (HR = 0.401; P = 0.026) with a median OS extending from 22.3–51.3 months (P = 0.019). Clinically, TD serves as an early-warning indicator for BVI-negative patients or patients without a pancreatobiliary signature, providing an actionable biomarker for postoperative chemotherapy selection. This finding facilitates identifying potential high-risk cohorts and establishes new foundations for precision prognostic stratification.

Several limitations to the current study warrant emphasis. Considering that this study had a single-center retrospective and non-randomized design, the demonstrated associations cannot be interpreted as causative. Second, the unclassified group may reflect underlying tumor heterogeneity or distinct biological behaviors with molecular characteristics and clinical implications warranting further investigation. Third, given the rarity of AAC in this study, certain analyses may be subject to statistical power constraints. Finally, this study did not use neoadjuvant therapy, which is an important procedure to improve OS. Corollary studies may enroll additional patients, launch multicenter, randomly assigned groups, and record more parameters and risk factors. In summary, this study identifies high-risk features in AAC post-surgery and establishes TD as a key biomarker for adjuvant chemotherapy efficacy. The BVI-/TD+ occult high-risk subgroup derives the most significant survival benefit from adjuvant therapy. The findings address an NCCN guideline gap and provide a new paradigm for precision treatment in this rare cancer.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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