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ORIGINAL ARTICLE

Retrospective Study

Comparison of clinical characteristics and prognostic factors in two site-specific categories of ampullary cancer

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Abstract

BACKGROUND

Ampullary cancer is a relatively rare malignant tumor in the digestive system. Its incidence has increased in recent years. As for now, its biological characteristics have not been fully clarified. Recent studies have primarily focused on the histological classification and genetic changes, but there are fewer investigations into the differences among site-specific subgroups. The clinicopathological characteristics of ampullary cancer occurring in different positions have not been elucidated. Furthermore, the role of adjuvant therapy in the treatment of patients with ampullary cancer remains controversial.

AIM

To study the clinicopathological features of the two site-specific subgroups of ampullary cancer and explore the factors affecting prognosis.

METHODS

A total of 356 patients who met the inclusion and exclusion criteria were enrolled. Patients were divided into ampulla of Vater cancer (AVC) and duodenal papilla cancer (DPC) based on the gross and microscopic findings. Baseline data, admission examination results, and perioperative outcomes were collected and analyzed. The Kaplan-Meier curve was used for survival analysis. Univariate and multivariate analysis was performed to explore the independent risk factors affecting the overall survival (OS) of both groups.

RESULTS
The preoperative total bilirubin level in patients with AVC was significantly higher than those with DPC (P = 0.04). The OS for patients with DPC was 58.90 ± 38.74 months, significantly longer than 44.31 ± 35.90 months for patients with AVC (P < 0.01). The independent risk factors affecting the OS of AVC included: Preoperative albumin level (P = 0.009), total bilirubin level (P = 0.017), and number of positive lymph nodes (P = 0.005). For DPC, risk factors included: Age (P = 0.004), tumor size (P = 0.023), number of positive lymph nodes (P = 0.010) and adjuvant treatment (P = 0.020). Adjuvant therapy significantly improved the OS rate of patients with DPC, but not for those with AVC.

CONCLUSION
Patients with AVC had a shorter OS compared to those with DPC. The prognosis factors and the role of adjuvant therapy of two groups were different.

Key Words: Ampullary cancer; Prognosis; Risk factors; Overall survival; Adjuvant therapy

Core Tip: Ampullary cancer research is crucial due to its increasing incidence. This study differentiates ampullary cancer types based on its primary site, showing that ampulla of Vater cancer (AVC) patients have shorter overall survival than duodenal papilla cancer (DPC) patients. Prognosis for AVC may be affected by serum albumin, total bilirubin, and positive lymph nodes. For DPC patients, age, tumor size, and lymph node positivity are linked to worse outcomes, with adjuvant therapy potentially improving prognosis. The findings offer doctors valuable insights for managing both cancer types.

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INTRODUCTION

The ampulla of Vater was first described in 1543 by Dr Wackwitz[1]. Cancer at this site is classified into distinct categories according to recently refined definitions: It qualifies as ampullary cancer if it is centered on the ampulla/major papilla and complies with, one of four recognized categories. On the contrary, it is deemed non-ampullary if more than 75% of the tumor mass is located beyond the ampulla[2]. There are obvious differences in the molecular biological characteristics of tumors originating from different areas around the ampulla[3,4]. Compared to cancers of the distal bile duct and pancreatic head, ampullary cancer typically affords a relatively satisfactory overall survival (OS) rate[5,6]. Despite of its low overall incidence which is less than 1% of all digestive system tumors[7-9], its prevalence has been increasing, posing a growing threat to public health[9].

Currently, for treatment for ampullary cancer, a comprehensive approach is typically used, including surgery, adjuvant therapy, neoadjuvant therapy and targeted therapy. Radical pancreaticoduodenectomy (PD) is prescribed for non-metastatic cases[10]. Adjuvant regimens are mainly selected based on different histological subtypes; and pancreato-biliary type usually follows protocols for cholangiocarcinoma or pancreatic cancer, whereas intestinal type might be treated similarly to colon cancer. Survival rates vary markedly across different studies. For ampullary cancer, the five-year survival rate ranges from 10% to 75% in the localized stage and 4.7% in the metastatic stage[7,11,12]. To date, the specific clinicopathological and biological traits of ampullary cancer remain insufficiently understood, and standardized diagnosis and treatment guidelines have yet to be established.

According to previous refined definitions[2], ampullary cancer is divided into four types based on the primary site: Intra-ampullary papillary-tubular neoplasm with invasion (Intra-AMP), ampullary-ductal, periampullary-duodenal and ampullary-not otherwise specified (NOS). Clinical characteristics and long-term survival outcomes differ among these classes. This study aims to consolidate the Intra-AMP and ampullary-ductal categories under term "ampulla of Vater cancer (AVC)", while designating the remaining as "duodenal papilla cancer (DPC)". By analyzing the data from our center, we intend to provide more detailed insights into the clinicopathological characteristics and biological traits of site-specific ampullary cancer as well as prognosis factors in OS, thereby aiding in the optimization of clinical diagnostics and therapeutic strategies for ampullary cancer.

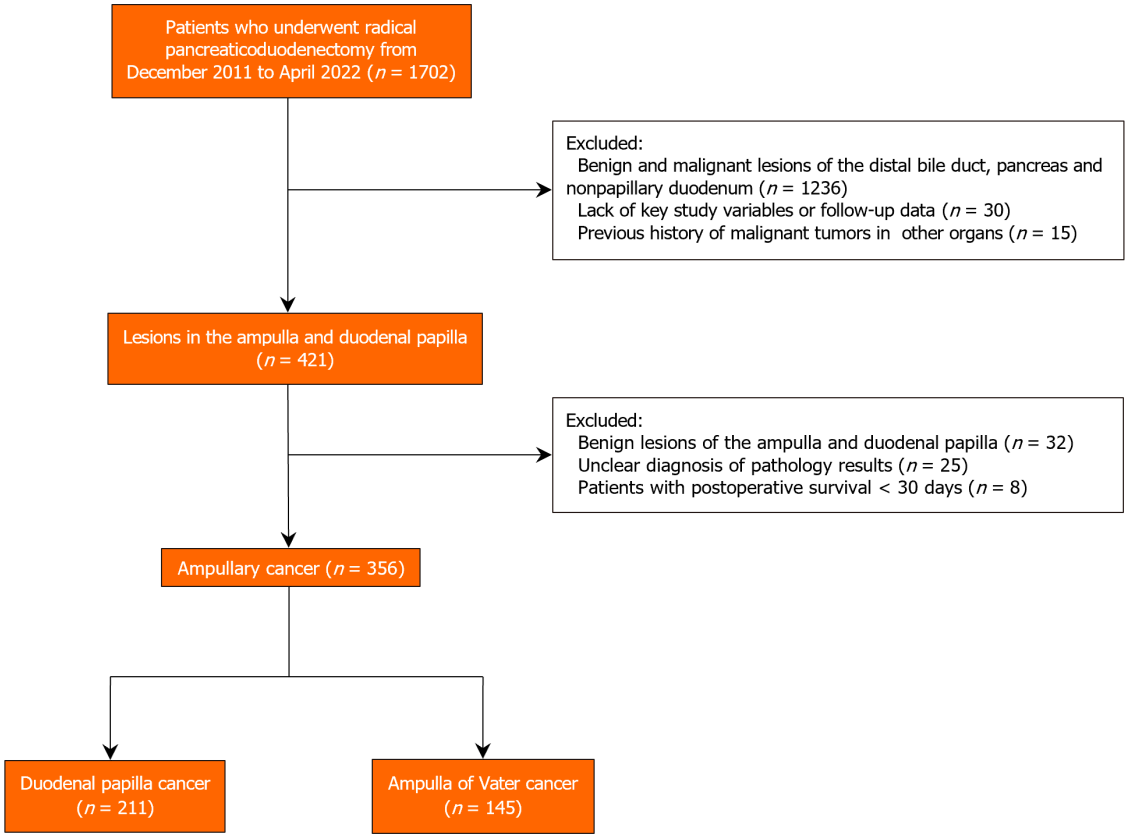

Figure 1 The flowchart of case selection.

MATERIALS AND METHODS

Study population and data collection

A total of 1702 patients who underwent PD at the Department of Bilio-pancreatic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, from October 2011 to April 2022, were retrospectively collected from the electronic medical record system. We excluded patients according to the following criteria: (1) Those with benign and malignant lesions at the distal bile duct, pancreas, and non-papillary parts of the duodenum; (2) Those with a history of malignant tumors in other parts of the body; (3) Those who died within 30 days after radical PD; (4) Those with missing key data or lost to follow-up; (5) Those with undetermined pathological results; and (6) Those with benign lesions of the ampulla and duodenal papilla. After the application of the exclusion criteria, a total of 356 patients diagnosed with ampullary cancer remained. They were subsequently categorized into two groups: 145 patients with AVC and 211 patients with DPC. The case selection process is depicted in Figure 1.

The collected data encompassed demographic characteristics, relevant preoperative laboratory test results, perioperative metrics, postoperative complications, use of adjuvant therapy, and OS of patients. Additional details obtained from postoperative pathology included tumor type, tumor size, status of surgical margin, TNM stage (according to the 8th edition American Joint Committee on Cancer), and the number of positive lymph nodes. The follow-up deadline was April 1, 2023, with OS calculated from the initial surgery date to the date of death from any cause.

Definition of AVC and DPC

Ampullary cancer was classified into four groups according to a previous study[2]. In our study, AVC, including Intra-AMP and ampullary-ductal groups from prior definitions, was identified when tumor tissue was mainly located in the ampullary duct or at the end of the common bile duct (CBD) and the opening of the pancreatic duct. DPC was defined as tumor tissue on the duodenal surface near or originating from the duodenal papilla, comprising two groups: Periampullary-duodenal and ampullary- NOS. All surgeries were performed by skilled surgeons, and pathology results were reviewed by seasoned senior pathologists. The preliminary differentiation between AVC and DPC is based on preoperative imaging examinations, such as abdominal enhanced computed tomography scans, magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP), in which EUS and ERCP can be used to clearly distinguish the type of cancer before surgery. The postoperative pathological examination is the gold standard to determine the type of ampullary cancer.

Calculation of relevant inflammatory indicators

Inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI) were derived with the formulas below: NLR = neutrophil count (× 10^9/L)/lymphocyte count (× 10^9/L). PLR = blood platelet count (× 10^9/L)/lymphocyte count (× 10^9/L). PNI = serum albumin (g/L) + 5 × lymphocyte count (× 10^9/L).

Statistical analysis

Continuous variables were presented as mean ± SD or median with interquartile range, according to their distribution. Qualitative variables were reported as frequencies and percentages. Categorical variables were compared according to the number of samples in the group using Pearson χ^2 or Fisher's exact tests, as appropriate. For the comparison of continuous variables, independent sample *t*-tests or Kruskal-Wallis *H* tests were employed, depending on whether the samples adhered to a normal distribution. We considered $P < 0.05$ to be statistically significant. Survival outcomes regarding OS between categories were evaluated using the Kaplan Meier method and compared by the log-rank test. The receiver operating characteristic curve was used to calculate optimal cutoff values for predictors, transforming continuous variables into categorical variables in two groups. Univariate Cox regression analysis was used to estimate hazard ratio (HR) and 95% confidence interval (CI) for OS, and variables with $P < 0.05$ were included in the multivariate Cox analysis. The method of mean interpolation was used to fill in missing values. Statistical analysis was conducted using SPSS 29.0 (SPSS, Inc., Chicago, IL, United States).

RESULTS

Demographic and clinicopathological characteristics

The median age was 59 (range: 52-64) for patients with AVC, which was 58 (range: 52-64) for those with DPC. There was no statistical difference in age ($P = 0.78$) between the two groups. The sex distribution comprised 51.7% males ($n = 75$) and 48.3% females ($n = 70$) in the AVC group, and 50.2% males ($n = 106$) and 49.8% females ($n = 105$) in the DPC group, with no significant variance in sex ratios between the two cancers ($P = 0.78$). Preoperative data analysis revealed a notably higher bilirubin level in AVC patients upon admission compared to that in those with DPC (117.19 ± 112.85 *vs* 88.57 ± 93.8 μmol/L, $P = 0.04$), while no statistically meaningful difference was found in neutrophil and lymphocyte counts, platelet count, albumin level, alanine aminotransferase, aspartate aminotransferase, and the American Society of Anesthesiologists score. The inflammation markers calculated based on preoperative lab results NLR, PLR, and PNI revealed no significant statistical difference between the two conditions. These demographic and clinicopathological characteristics are summarized in Table 1.

Perioperative outcomes

The average duration of surgery for the AVC group was 353.57 ± 998.74 minutes, slightly longer than 339.45 ± 107.36 minutes for the DPC group. Both groups showed comparable results regarding intraoperative blood loss and length of postoperative hospital stay. The majority of surgeries achieved negative surgical margins, with only 3 AVC patients and 2 DPC patients presenting with positive margins. The maximum tumor diameter and the number of positive lymph nodes were slightly higher in the DPC group compared to those in the AVC group (1.9 ± 1.71 cm *vs* 1.7 ± 1.5 cm; 0.82 ± 2.6 *vs* 0.62 ± 1.2, respectively), yet these differences did not reach statistical significance ($P = 0.59$ and $P = 0.83$, respectively). Delayed gastric emptying, a significant postoperative complication, was observed in 62.8% of AVC patients and 57.8% of DPC patients. Other complications such as pancreatic fistula, postoperative bleeding, and infection occurred at relatively low frequencies, with no significant difference between groups. Approximately 20% of patients in both groups received postoperative adjuvant therapy, involving diverse regimens such as tegafur, gimeracil, oteracil potassium capsule (either as monotherapy or combination with oxaliplatin and gemcitabine), gemcitabine monotherapy or combination with capecitabine, albumin-paclitaxel, and oxaliplatin monotherapy. Remarkably, the OS time significantly differed between the groups, with DPC patients demonstrating a superior survival rate (58.90 ± 38.74 months) compared to AVC patients (44.31 ± 35.90 months). Detailed perioperative outcomes are presented in Table 2.

Kaplan-Meier survival curves

The survival analysis indicated that AVC patients had a lower OS rate compared to their DPC counterparts (Figure 2). The 5-year survival rate for patients with AVC was 63%, while the 5-year survival rate for those with DPC was higher, at 76%. Following surgical intervention, the average survival time for patients with AVC cancer was 93.6 months, compared to 107.5 months for patients with DPC. Overall, AVC presented a worse prognosis than DPC. Specifically, AVC patients with preoperative albumin levels > 38.45 g/L, preoperative total bilirubin levels ≤ 28.4 μmol/L, and ≤ 1 positive lymph node exhibited relatively improved OS (Figure 3). Conversely, DPC patients aged > 60 years, with tumor size > 2.35 cm, and ≥ 2 lymph nodes, and those who did not receive adjuvant therapy, showed poorer OS (Figure 4).

Outcomes of univariate and multivariate analysis

The univariate analysis incorporated all potential factors affecting the OS of AVC and DPC patients. Significant factors for AVC included lymphocyte count ($P = 0.048$, HR = 1.812, 95%CI: 1.006-3.262), platelet count ($P = 0.03$, HR = 2.083, 95%CI: 1.074-4.039), preoperative albumin ($P = 0.045$, HR = 1.840, 95%CI: 1.015-3.336), total bilirubin level upon admission ($P = 0.035$, HR = 0.440, 95%CI: 0.205-0.945), and the number of positive lymph nodes ($P = 0.009$, HR = 0.407, 95%CI: 0.208-

Table 1 Demographic data and clinical outcomes of ampulla of Vater cancer and duodenal papilla cancer, *n* (%)

Variables	AVC (*n* = 145)	DPC (*n* = 211)	*P* value
Age, year	59 (52-64)	58 (52-64)	0.78
≤ 60	88 (60.7)	125 (59.2)	
> 60	57 (39.3)	86 (40.8)	
Sex			0.78
Male	75 (51.7)	106 (50.2)	
Female	70 (48.3)	105 (49.8)	
BMI, kg/m^2			0.50
< 18.5	11 (8.1)	24 (12.1)	
18.5-24	96 (71.1)	133 (67.2)	
≥ 24	28 (20.8)	41 (20.7)	
Diabetes			0.74
Yes	9 (6.2)	15 (7.1)	
No	136 (93.8)	196 (92.9)	
Neutrophil count, × 10^9/L	4.17 ± 2.3	4.15 ± 2.3	0.9
Lymphocyte count, × 10^9/L	1.34 ± 0.4	1.36 ± 0.5	0.88
Blood platelet count, × 10^9/L	259.89 ± 97.7	251.42 ± 90.8	0.28
Albumin, g/L	35.83 ± 4.80	36.46 ± 4.5	0.35
Tbil, μmol/L	117.19 ± 112.9	88.57 ± 93.8	0.04[a]
ALT, U/L	138.34 ± 136.5	128.97 ± 109.9	0.77
AST, U/L	112.73 ± 110.1	100.39 ± 84.7	0.93
CA19-9, U/mL	433.35 ± 1405.4	499.65 ± 1807.2	0.61
NLR	3.49 ± 2.42	3.59 ± 3.28	0.86
PLR	215.32 ± 116	205.33 ± 103.43	0.55
PNI	41.99 ± 7.1	42.67 ± 7.34	0.39
ASA			0.10
I	12 (8.3)	26 (12.3)	
II	101 (69.7)	155 (73.5)	
III	32 (22.1)	30 (14.2)	

[a]$P < 0.05$.

BMI: Body mass index; Tbil: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; PNI: Prognostic nutritional index; ASA: American Society of Anesthesiologists; AVC: Ampulla of Vater cancer; DPC: Duodenal papilla cancer.

0.796). For DPC, statistically significant variables included age, preoperative lymphocyte count, preoperative albumin level, total bilirubin level upon admission, PLR, PNI, serum CA19-9 level, N stage, TNM stage in the 8th edition of AJCC, tumor size, the number of positive lymph nodes, and adjuvant therapy. Multivariate analysis, focusing on variables with $P < 0.05$, identified independent risk factors for AVC and DPC prognosis. For AVC, these were preoperative albumin level, admission bilirubin level upon admission, and the number of positive lymph nodes. For DPC, significant factors included age, tumor size, the number of positive lymph nodes, and adjuvant treatment. The outcomes of these analysis are detailed in Tables 3 and 4.

DISCUSSION

The accurate determination of a tumor's origin site is pivotal in selecting appropriate treatment strategies and in prognosis evaluations. The ampulla of Vater represents a complex anatomical area encompassing various compartments,

Table 2 Perioperative outcomes of ampulla of Vater cancer and duodenal papilla cancer, *n* (%)

Variables	AVC (*n* = 145)	DPC (*n* = 211)	*P* value
Duration of surgery, min	350 (290-420)	324.5 (256.3-413)	0.16
Intraoperative blood loss, mL	275 (100-400)	275 (100-500)	0.76
Postoperative hospital stay, day	22.32 ± 9.8	21.96 ± 9.5	0.72
Surgical margin			0.67
Negative	142 (97.9)	209 (99.1)	
Positive	3 (2.1)	2 (0.9)	
TNM stage			0.58
I	68 (62.4)	126 (68.1)	
II	31 (28.4)	46 (24.9)	
III	10 (9.2)	13 (7.0)	
Tumor size, cm	1.7 ± 1.5	1.9 ± 1.7	0.59
Number of positive lymph nodes			0.83
≤ 1	118 (84.3)	166 (83.4)	
≥ 2	22 (15.7)	33 (16.6)	
Delayed gastric emptying			0.35
Yes	91 (62.8)	122 (57.8)	
No	54 (37.2)	89 (42.2)	
Pancreas fistula			0.74
Yes	43 (29.7)	66 (31.3)	
No	102 (70.3)	145 (68.7)	
Postoperative hemorrhage			0.67
Yes	8 (5.5)	14 (6.6)	
No	137 (94.5)	197 (93.4)	
Postoperative infection			0.87
Yes	5 (3.4)	8 (3.8)	
No	140 (96.6)	203 (96.2)	
Adjuvant therapy			0.72
Yes	28 (19.3)	44 (20.9)	
No	117 (80.7)	167 (79.1)	
Overall survival, month	44.3 ± 35.9	58.9 ± 38.7	< 0.01[a]

[a]*P* < 0.05.

TNM: Tumor node metastasis; AVC: Ampulla of Vater cancer; DPC: Duodenal papilla cancer.

each lined with distinct types of epithelia and presenting a multifaceted environment. Despite their proximal locations, significant disparities exist in the biological properties and tumor behaviors among tumors emanating from different periampullary tissues. This differentiation holds even for tumors within the same organ, exemplified by the clinical-pathological and molecular variances observed between tumors in the pancreatic head *vs* those in the pancreatic body and tail[13,14]. Prior investigations have revealed that, in comparison to pancreatic head cancers, KRAS and SMAD4 genetic alterations were markedly more prevalent in pancreatic body/tail cancers, indicating a greater malignancy in the latter[15]. These insights underscored the significance of tumor location as a critical aspect of research endeavors. Vo *et al* [16] categorized ampullary tumors into four distinct groups, showcasing significant variations in tumor size, depth of invasion, and T stage. However, this classification scheme proves to be rather cumbersome for clinical application. Building upon this, we simplified the classification into two subtypes based on gross and microscopic observations: AVC and DPC, facilitating a comparative study utilizing data from our center.

Table 3 Univariate and multivariate Cox regression analysis of ampulla of Vater cancer

Characteristics	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex (male/female)	1.079 (0.600-1.938)	0.800		
Age (≤ 60/> 60), year	0.877 (0.485-1.586)	0.664		
BMI, kg/m^2				
< 18.5		Reference		
18.5-24	1.256 (0.298-5.298)	0.756		
> 24	1.876 (0.414-8.494)	0.414		
Diabetes (yes/no)	1.048 (0.253-4.348)	0.949		
Neutrophil count (≤ 5.39/> 5.39), × 10^9/L	2.434 (0.961-6.168)	0.061		
Lymphocyte count (≤ 1.21/> 1.21), × 10^9/L	1.812 (1.006-3.262)	0.048[a]	1.849 (0.969-3.529)	0.062
Blood platelet count (≤ 165/> 165), × 10^9/L	2.083 (1.074-4.039)	0.030[a]	1.791 (0.893-3.591)	0.101
Albumin (≤ 38.45/> 38.45), g/L	1.840 (1.015-3.336)	0.045[a]	2.387 (1.247-4.569)	< 0.01[a]
ALT (≤ 283/> 283), U/L	0.369 (0.114-1.192)	0.096		
AST (≤ 277/> 277), U/L	0.437 (0.106-1.803)	0.252		
Tbil (≤ 28.4/> 28.4), μmol/L	0.440 (0.205-0.945)	0.035[a]	0.343 (0.143-0.825)	0.017[a]
NLR (≤ 5.90/> 5.90)	0.181 (0.025-1.315)	0.091		
PLR (≤ 186.6/> 186.6)	0.737 (0.408-1.332)	0.312		
PNI (≤ 44.6/> 44.6)	0.664 (0.363-1.214)	0.183		
CA19-9 (≤ 37.54/> 37.54), U/mL	1.258 (0.690-2.291)	0.454		
ASA				
I		Reference		
II	0.536 (0.223-1.288)	0.163		
III	0.633 (0.225-1.786)	0.388		
T stage				
T1		Reference		
T2	1.641 (0.811-3.321)	0.168		
T3	1.354 (0.392-4.679)	0.632		
N stage				
N0		Reference		
N1	1.389 (0.642-3.005)	0.404		
N2	1.524 (0.355-6.529)	0.571		
TNM stage				
I		Reference		
II	1.142 (0.516-2.526)	0.743		
III	2.413 (0.959-6.072)	0.061		
Duration of surgery (≤ 368/> 368), min	0.853 (0.471-1.544)	0.599		
Intraoperative blood loss (280 ≤ /> 280), mL	0.895 (0.464-1.726)	0.741		
Tumor size (≤ 1.99/> 1.99), cm	0.475 (0.210-1.072)	0.073		
Number of positive lymph nodes (≤ 1/≥ 2)	0.407 (0.208-0.796)	< 0.01[a]	0.375 (0.189-0.745)	< 0.01[a]

Adjuvant therapy (yes/no)	0.988 (0.475-2.053)	0.974

[a]*P* < 0.05.

BMI: Body mass index; Tbil: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; PNI: Prognostic nutritional index; ASA: American Society of Anesthesiologists; AVC: Ampulla of Vater cancer; DPC: Duodenal papilla cancer.

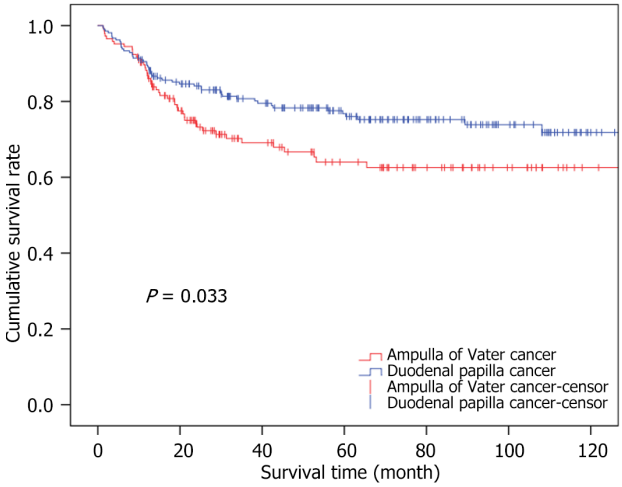

Figure 2 Kaplan-Meier curve of overall survival between ampulla of Vater cancer and duodenal papilla cancer.

This research is a single-center, observational study focusing on individuals who underwent radical PD and were subsequently diagnosed with ampulla of Vater or DPC *via* postoperative pathology and follow-up examinations. comparison of baseline data revealed that the bilirubin levels in patients with AVC were substantially higher than those in patients with DPC (117.19 ± 112.85 *vs* 88.57 ± 93.80 μmol/L, $P = 0.04$). Furthermore, the average survival duration of DPC patients exceeded that of AVC patients (58.90 ± 38.74 *vs* 44.31 ± 35.90 months, $P < 0.01$), with 1-year, 3-year, and 5-year survival rates for AVC standing at 91%, 83%, and 74% respectively, compared to 94%, 86%, and 83% for DPC.

Tumors in AVC primarily localize within the ampullary duct. As these tumors enlarge, they can obstruct the communal outflow pathways of the bile and pancreatic ducts early on, leading to symptoms like jaundice, cholangitis, and potentially pancreatitis. Conversely, DPC generally originates from the duodenal mucosa. With progressive growth and submucosal invasion, these tumors may compress the CBD and the shared channel opening, thus precipitating jaundice. Consequently, jaundice symptoms in patients with DPC tend to manifest later and are less severe compared to those with AVC.

Ampullary cancer can be divided into two types based on immunohistochemical characteristics: The intestinal type and the pancreatobiliary type. The intestinal type predominantly expresses intestinal immune markers such as CDX2, MUC2, and CK20. On the contrary, the pancreatobiliary type typically exhibits positive staining for markers including MUC1, MUC5AC, and CK7, analogous to pancreatic cancer and cholangiocarcinoma[17,18]. Studies have shown that cases identified as pancreatobiliary whether purely pancreatobiliary or mixed with predominantly pancreatobiliary features exhibit shorter OS compared to those classified as purely intestinal or mixed with predominantly intestinal traits [19,20]. In our study, OS for patients with ampullary cancer was significantly shorter than that for patients with DPC. This outcome may be attributed to the predominance of pancreatobiliary and mixed histological types in the former group. Previous studies often overlooked detailed classification of ampullary cancer's histological subtypes, resulting in limited data availability. Thus, additional research is necessary for further exploration and verification.

Ampullary carcinoma exhibits significant heterogeneity. In addition to immunohistochemical typing, advancements in sequencing technology and genomics have further elucidated the biological characteristics of ampullary tumors at the molecular level. Recent studies[21-23] indicate that the frequency of KRAS mutations is relatively high in pancreatobiliary subtypes, while mutations in the PI3/AKT pathway are more prevalent in intestinal subtypes. However, the patterns of genomic alterations across different subtypes still necessitate research and verification using large sample sizes, and the prognostic implications of these alterations in various histological subtypes of ampullary carcinoma remain to be fully established. Future investigations should integrate clinical pathological typing, histological classification, and genetic changes to identify new therapeutic targets for ampullary carcinoma, ultimately leading to the development of more personalized diagnosis and treatment strategies aimed at enhancing the consistency of treatment outcomes.

Previous studies investigating the prognostic factors affecting OS in ampullary cancer seldom included subgroup analysis based on site-specific conceptual groupings. In contrast, our study divided cases into two subgroups according to the aforementioned classifications, enabling a more precise and meticulous evaluation of prognostic factors. Our findings indicate distinct differences in prognostic risk factors between the two subgroups, despite both being forms of ampullary cancer. While the number of lymph node involvements is a common prognosis factor for both, distinct

Table 4 Univariate and multivariate Cox regression analysis of duodenal papilla cancer

Characteristics	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex (male/female)	1.226 (0.698-2.154)	0.478		
Age (≤ 60/> 60), year	0.461 (0.262-0.811)	0.007[a]	0.372 (0.189-0.733)	0.004[a]
BMI, kg/m^2				
< 18.5		Reference		
18.5-24	0.693 (0.306-1.569)	0.380		
> 24	0.375 (0.126-1.120)	0.079		
Diabetes (yes/no)	3.832 (0.529-27.767)	0.184		
Neutrophil count (≤ 2.815/> 2.815), × 10^9/L	1.751 (0.991-3.096)	0.054		
Lymphocyte count (≤ 1.395/> 1.395), × 10^9/L	2.910 (1.486-5.698)	0.002[a]	2.446 (0.932-6.418)	0.069
Blood platelet count (≤ 196.5/> 196.5), × 10^9/L	1.556 (0.870-2.782)	0.136		
Preoperative albumin (≤ 32.5/> 32.5), g/L	2.579 (1.431-4.647)	0.002[a]	2.266 (0.666-7.711)	0.191
ALT (≤ 114.5/> 114.5), U/L	0.633 (0.361-1.109)	0.110		
AST (≤ 51.5 /> 51.5), U/L	0.575 (0.287-1.153)	0.119		
Tbil (≤ 27.25/> 27.25), μmol/L	0.354 (0.166-0.755)	0.007[a]	0.634 (0.248-1.619)	0.341
NLR (≤ 3.21/> 3.21)	0.663 (0.376-1.171)	0.157		
PLR (≤ 184.92/> 184.92)	0.539 (0.306-0.949)	0.032[a]	0.734 (0.334-1.614)	0.442
PNI (≤ 36.98/> 36.98)	2.333 (1.216-4.476)	0.011[a]	0.315 (0.072-1.379)	0.125
CA19-9 (≤ 143.9/> 143.9), U/mL	0.414 (0.235-0.731)	0.002[a]	0.808 (0.389-1.678)	0.567
ASA				
I		Reference		
II	0.540 (0.220-1.290)	0.160		
III	0.630 (0.230-1.790)	0.380		
T stage				
T1		Reference		
T2	1.740 (0.949-3.189)	0.073		
T3	2.601 (0.610-11.088)	0.196		
N stage				
N0		Reference		
N1	2.154 (1.128-4.113)	0.020[a]	0.800 (0.201-3.189)	0.752
N2	3.123 (0.942-10.354)	0.063	0.365 (0.038-3.554)	0.386
TNM stage				
I	-	Reference		
II	1.948 (1.001-3.790)	0.050	1.973 (0.598-6.516)	0.265
III	4.344 (1.856-10.165)	0.001[a]	3.247 (0.402-26.228)	0.269
Duration of surgery, min (≤ 351/> 351)	1.791 (0.982-3.266)	0.058		
Intraoperative blood loss, mL (305 ≤/> 305)	0.802 (0.454-1.414)	0.445		
Tumor size (≤ 2.35/> 2.35), cm	0.463 (0.263-0.816)	0.008[a]	0.436 (0.213-0.893)	0.023[a]
Number of positive lymph nodes (≤ 1/≥ 2)	0.446 (0.230-0.865)	0.017[a]	0.328 (0.141-0.767)	0.010[a]
Adjuvant therapy (yes/no)	0.253 (0.079-0.815)	0.021[a]	0.233 (0.068-0.797)	0.020[a]

[a]*P* value < 0.05.

BMI: Body mass index; Tbil: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; PNI: Prognostic nutritional index; ASA: American Society of Anesthesiologists.

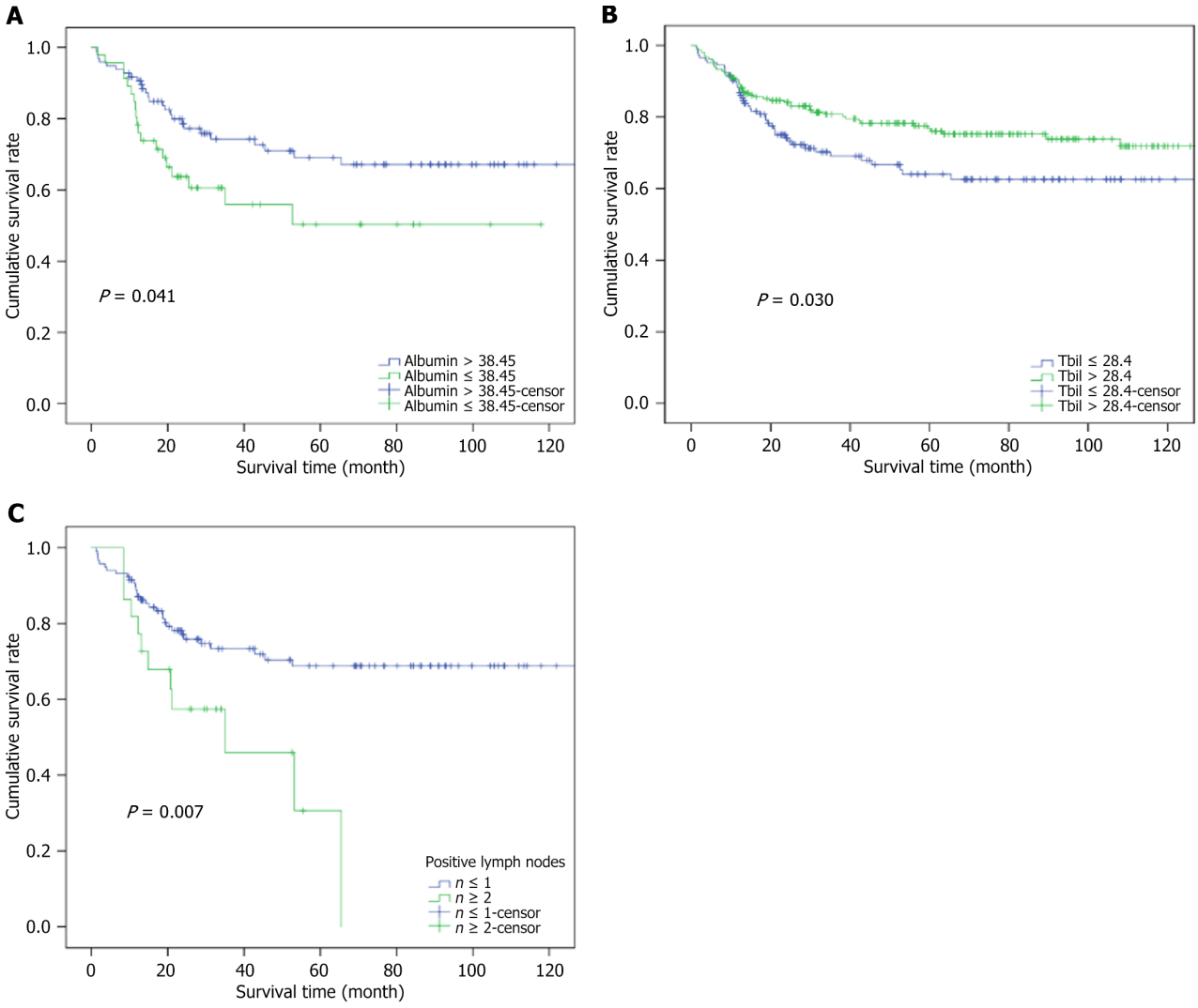

Figure 3 Kaplan-Meier survival curves for the impact of three risk factors on the overall survival of ampulla of Vater cancer. A: Kaplan-Meier survival curve for the impact of preoperative albumin on the overall survival of ampulla of Vater cancer (AVC); B: Kaplan-Meier survival curve for the impact of preoperative total bilirubin on the overall survival of AVC; C: Kaplan-Meier survival curve for the impact of the number of positive lymph node on the overall survival of AVC. Tbil: Total bilirubin.

independent risk factors were identified: Preoperative albumin and bilirubin levels in AVC, and age, tumor size, and adjuvant treatment in DPC. Such distinctions point to novel insights.

Serum albumin is an important bioactive substance involved in human metabolism, and its clinical use in indicating inflammatory processes, nutritional status, and prognosis in cancer patients has been widely described[24,25]. It can also be used in conjunction with the triceps skinfold sum to predict mortality in cancer patients effectively[26]. In our study, pre-admission serum albumin level emerged as an independent risk factor for OS in patients with DPC. Patients with an albumin level ≤ 38.45 g/L faced a 1.387 times greater risk of mortality compared to those with level > 38.45 g/L. However, this association was not observed in patients with AVC.

Serum bilirubin level is crucial in testing liver function. Elevated bilirubin levels are generally associated with disease progression and poorer prognosis[27,28]. Our study demonstrates that, for patients with AVC, high serum total bilirubin levels independently risk OS. Patients with lower bilirubin levels exhibited approximately a 65% reduced mortality risk compared to those with higher levels (P = 0.017, HR = 0.343, 95%CI: 0.143-0.825). This correlation was not observed in patients with DPC. Notably, serum bilirubin levels upon admission were significantly lower in patients with DPC than in those with AVC, indicating a lesser impact on liver function. Although the univariate analysis showed statistical significance for total bilirubin levels, the multivariate Cox regression results, which included numerous variables, might have bias. Further research is necessary to determine whether total bilirubin levels have prognosis significance in DPC patients.

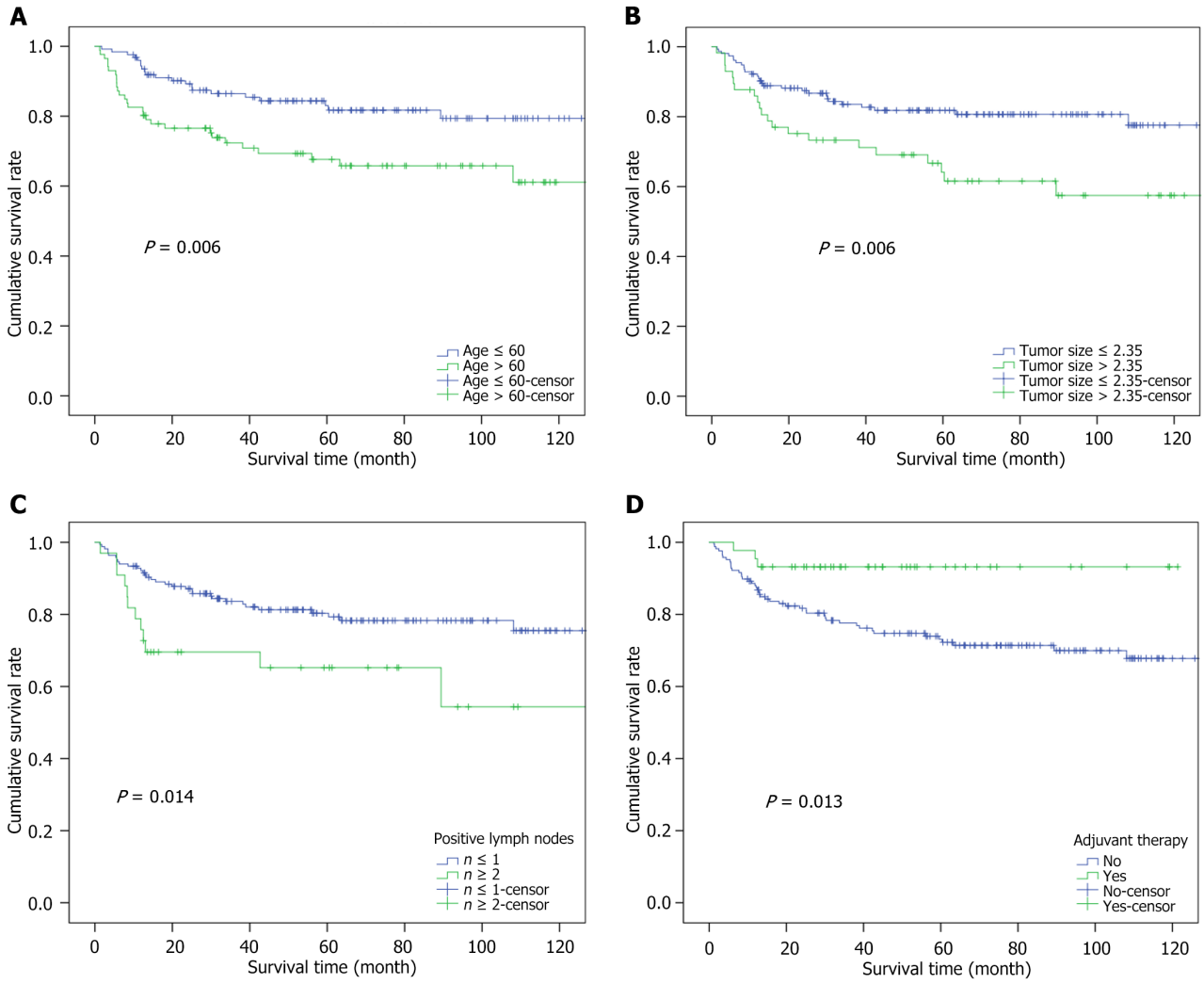

Figure 4 Kaplan-Meier survival curves for the impact of four risk factors on the overall survival of duodenal papilla cancer. A: Kaplan-Meier survival curve for the impact of age on the overall survival of duodenal papilla cancer (DPC); B: Kaplan-Meier survival curve for the impact of tumor size on the overall survival of DPC; C: Kaplan-Meier survival curve for the impact of the number of positive lymph nodes on the overall survival of DPC; D: Kaplan-Meier survival curve for the impact of adjuvant therapy on the overall survival of DPC.

Compared with earlier studies, our center's data revealed improved survival outcomes for both AVC and DPC, perhaps due to our strategy of treating hyperbilirubinemia before performing PD. Current evidence robustly supports using ERCP as the primary approach for preoperative biliary drainage, with metal stents proving superior to plastic ones [29-31]. The management of preoperative jaundice, especially in the context of PD, is critical as it significantly influences surgical results and postoperative complications[30].

Furthermore, lymph node involvement is a well-known prognosis factor in malignant tumors. We categorized patients based on the number of positive lymph nodes, revealing that individuals with ≤ 1 positive node had over a 60% lower mortality risk in both AVC and DPC subgroups compared to those with ≥ 2 positive nodes. The significance of lymph node count as an independent risk factor for OS in both cancer types aligns with findings from previous studies[32,33]. Our research varied from the traditional TNM staging by using 1 as a threshold for grouping, which underscored differences in OS between groups and might inform future clinical staging of ampullary cancer. However, the limited sample size constrained detailed lymph node group analysis; thus, larger datasets are needed for further exploration.

In this study, 72 patients underwent a complete regimen of postoperative adjuvant chemotherapy. Our findings indicate that adjuvant chemotherapy confers a notable survival advantage in patients with DPC (P = 0.02, HR = 0.233, 95%CI: 0.068-0.797), establishing it as an independent prognostic factor for OS in DPC. However, this benefit was not observed in patients with AVC. Adjuvant therapy constitutes a critical component of the comprehensive management strategy for ampullary cancer, though its effectiveness remains a point of contention. Despite numerous studies[34-36] revealing no significant advantage of adjuvant chemotherapy in enhancing the OS rates of ampullary cancer patients, a study conducted by the Mayo Clinic highlighted the positive impact of adjuvant chemotherapy in patients with advanced (stage IIB or higher) ampullary cancer[37]. This study reported that adjuvant therapy led to a roughly 55% decrease in mortality risk (P = 0.03, HR = 0.45, 95%CI: 0.22-0.93), translating to an almost 12-month survival benefit. Additionally, another retrospective study[38] corroborated the survival advantage of adjuvant therapy in individuals with ampullary cancer, with more pronounced benefits in those presenting with high-risk factors such as advanced T and N stages, poor

tumor differentiation, and positive resection margins. The 2023 NCCN Guidelines for Diagnostic and Therapeutic Management of Ampullary Cancer[39] endorse the role of adjuvant therapy, offering guidance on chemotherapy options and presenting a vital benchmark for the standardized care of ampullary cancer. The adjuvant chemotherapy protocols employed in this investigation varied widely over an extended period. The initial choice of chemotherapy regimens did not take histological subtypes into account, and not all patients completed their chemotherapy within the same institution, potentially skewing the evaluation of therapeutic benefits. Nonetheless, this study demonstrates the utility of adjuvant chemotherapy for certain patient cohorts, contributing meaningful insights to the ongoing discourse on adjuvant treatment strategies for ampullary cancer, particularly about site-specific subgroup classifications.

No prognosis significance was attributed to the TNM stage in the multivariable analysis conducted in this study, possibly due to the limited sample size and the potential bias introduced by variable interactions. Further research, involving large-scale, multi-center studies, is requisite to delve into the histological subclassifications, investigate histological biomarker differences between subgroups, and elucidate the disparate survival determinants in ampullary cancer.

Although this study is a single-center retrospective analysis with a limited sample size, it holds clinical and scientific significance. Our research enhances the understanding of the clinical pathological characteristics of ampullary cancer, enriches the existing literature, and serves as a reference for developing standardized diagnostic and treatment protocols for this condition, as well as for the application and selection of postoperative adjuvant therapies. In the future, we should conduct multicenter and large-sample prospective studies that incorporate immunohistochemical indicators and integrate molecular analysis.

CONCLUSION

In conclusion, AVC demonstrates shorter OS compared to DPC. There were significant differences in prognosis factors and the efficacy of adjuvant therapy between the two groups. However, adjuvant therapy appears to offer greater benefits to patients with DPC.

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FOOTNOTES

Author contributions: Zhang JZ and Zhang ZW have contributed equally to this work; Zhang JZ was responsible for to data curation, conceptualization, methodology, and writing the original draft; Zhang ZW wrote the original draft and performed formal data analysis; Guo XY and Zhu DS completed case collection, follow-up and preliminary data compilation; Huang XR revised the manuscript and provided clinical advice. Guo T and Yu YH were contributed equally to supervision, funding acquisition, writing-review and editing. First, the corresponding author, as the primary individual responsible for the article, oversees the selection of the topic, research design, and content review. Both Professor Yu YH and Dr Guo T shared these responsibilities throughout the study's implementation. They jointly agreed on the topic selection, collaboratively formulated the research plan, and provided equally significant support in executing the plan. Second, upon completion of the manuscript, both authors contributed unique insights regarding the depth of the content and the rigor of the conclusions. They collaboratively assisted in the correction and editing processes and finalized the preparation of the relevant submission materials. Their contributions were equivalent in importance. Third, during the ethical review of this article, both authors jointly prepared the necessary materials, demonstrating the ethical soundness of this study, which successfully passed the ethical approval process. This collaboration ensured the smooth progression of the research. Fourth, both authors provided equally crucial assistance in securing funding for this study. Given the substantial contributions made by both individuals to this article, they are designated as co-corresponding authors.

Institutional review board statement: The study was approved by the ethics committee of the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Informed consent statement: The acquisition and use of these clinical data were approved by the Institutional Review Board. After review by the ethics committee, a waiver of informed consent was granted for this subject.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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