Original Article

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Unveiling the unexplored secret: Aggressive behavior and poor survival in intrahepatic mucinous adenocarcinoma compared to conventional adenocarcinoma

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SUMMARY Intrahepatic bile duct mucinous adenocarcinoma (IHBDMAC) is a rare pathological subtype of intrahepatic cholangiocarcinoma (IHCC), and its tumor biological features and survival outcomes have rarely been explored, especially when compared to the most common subtype, intrahepatic bile duct adenocarcinoma (IHBDAC). Therefore, the aim of this study was to explore the clinical features and survival outcomes of IHBDAC and IHBDMAC using the Surveillance, Epidemiology, and End Results (SEER) database from 2000 to 2021. A total of 1,126 patients were included, with 1,083 diagnosed with IHBDAC and 43 diagnosed with IHBDMAC. Patients with IHBDMAC presented with a more advanced T stage (55.8% *vs.* 36.9%, $P = 0.012$) and higher rate of lymph node metastasis (37.2% *vs.* 24.9%, $P = 0.070$). Cox regression identified advanced T stage, lymph node metastasis, and distant metastasis as poor survival predictors, while chemotherapy and surgery were protective factors. Survival analyses revealed significantly worse overall survival (OS) and cancer-specific survival (CSS) for IHBDMAC compared to IHBDAC ($P < 0.05$). Even after matching, patients with IHBDMAC still had a worse prognosis than those with IHBDAC. These findings highlight the aggressive nature of IHBDMAC and the need for tailored therapeutic strategies. Future research should focus on prospective studies and molecular insights to develop targeted treatments for IHBDMAC.

Keywords mucinous adenocarcinoma, surgery, intrahepatic cholangiocarcinoma, prognosis

1. Introduction

Intrahepatic cholangiocarcinoma (IHCC) is the second most common primary liver malignancy, originating from the bile ducts within the liver. It represents a heterogeneous group of tumors with varying biological behaviors and clinical outcomes (*1*). For IHCC, surgical treatment achieving R0 resection has always been the cornerstone of therapy (*1*). In addition, recent studies have shown that adjuvant immunotherapy and targeted therapy can also significantly improve the prognosis of patients with this type of tumor (*2*). IHCC can be broadly classified into different histological subtypes, the most prominent of which are intrahepatic bile duct adenocarcinoma (IHBDAC) and intrahepatic bile duct mucinous adenocarcinoma (IHBDMAC) (*3*). IHBDAC is the most prevalent subtype and is characterized by tubular and glandular structures formed by malignant biliary epithelial cells. It has been extensively studied, with well-documented clinical features and prognostic factors. In contrast, IHBDMAC is less common and its clinic-pathological features have not been fully evaluated, especially when compared to IHBDAC. Distinct differences in these two different pathological subtypes are evident in HE-stained images. As shown in Figure 1, mucinous production is less prominent in IHBDAC (Figure 1A) while extensive mucinous production and the presence of mucin lakes are evident in IHBDMAC (Figure 1B). In addition, the cells in IHCC are tightly arranged with well-defined ductal or acinar structures, whereas the cells in IHBDMAC are loosely arranged with irregular glandular structures within the mucin lakes. Only Azchar *et al*. evaluated the prognostic value of mucinous component in patients with IHCC (*4*). However, further more in-depth analysis was not performed, especially in the post-matched cohort (*4*). According to the latest (8th) American Joint Committee on Cancer (AJCC) staging system, apart from three most conventional staging factors, including the T, N, and M stage, concurrent liver cirrhosis,

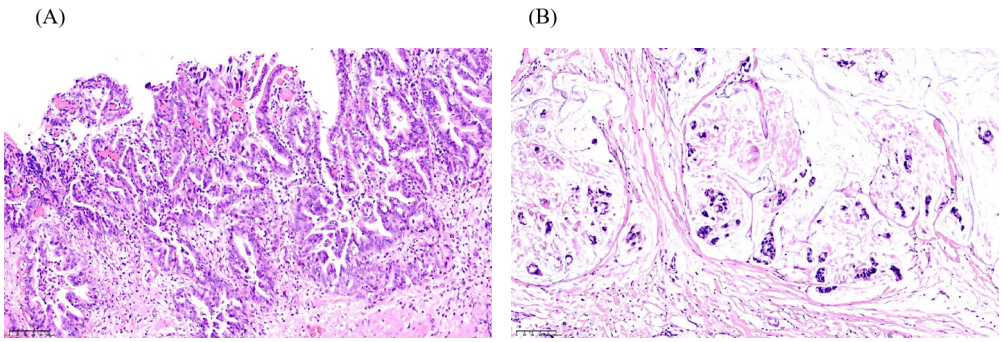

Figure 1. Representative images of pure IHBDAC and IHBDMAC (hematoxylin and eosin staining, 20×). A, pure adenocarcinoma; B, mucinous adenocarcinoma.

the serum CA199 level, and primary sclerosing cholangitis are cited as prognostic factors requiring additional clinical care. The prognostic significance of a mucinous component in IHCC is still being evaluated. Undoubtedly, understanding these differences is crucial to tailoring therapeutic strategies and improving patient management.

The Surveillance, Epidemiology, and End Results (SEER) database provides a valuable resource for examining large-scale cancer trends and outcomes. Utilizing this extensive database, the current study sought to perform a retrospective analysis to compare the clinical features and survival outcomes of patients with IHBDAC and IHBDMAC. Specifically, this study sought to identify distinct prognostic factors and treatment modalities that may influence survival in these two subtypes, thereby contributing to a more nuanced understanding of IHBDMAC and informing future clinical practice.

2. Materials and Methods

2.1. Patients

The SEER database is the largest publicly-available cancer database, covering almost 28% of the American population (*5*). Patients diagnosed with IHCC from the SEER database [released in April 2024: version 8.4.3; SEER 17 Regs Custom Data (with SEER Plus data, from 2000 to 2021)] were retrospectively reviewed and analyzed. The "Primary Site—labeled-liver/intrahepatic bile duct" variable was used to identify patients with tumors primarily located in the liver. The variable "behavior-malignant" was used to focus on malignancies. Only patients with pathologically confirmed IHBDAC or IHBDMAC were considered eligible. The pathologically diagnosed variables were restricted to "Positive histology." Given the similarities between the 7th edition and 8th edition of AJCC staging criteria for IHCC, cancers staged according to the 7th AJCC criteria [Derived AJCC TNM, 7th ed (2010-2015)] and the 8th AJCC criteria [Derived EOD 2018 TNM (2018+)] were combined. Consequently, T stages were broadly classified into T1-T2 and T3-T4, and N stages were similarly classified into node-negative (N-) and node-positive (N+). Moreover, only patients with survival information (greater than 0 months) were included.

2.2. Variable identification

A total of fourteen variables were identified for further analysis, including age, sex, race, marital status, T stage, N stage, pathological subtypes, tumor differentiation grade, radiotherapy, chemotherapy, cancer-related death (CRD), AFP level, and cirrhosis status. The continuous variable "Age" was categorized into ≤60 and >60. Minor adjustments were also applied to other categorical variables. For instance, marital status was simplified into two groups: married and single/unknown. Race was simplified into two major groups: white and other. Tumor differentiation status was simplified into three groups: well to moderately differentiated, poorly differentiated to undifferentiated, and unknown.

2.3. Study design

First, a basic comparison of clinicopathological features and long-term survival was made between patients with IHBDAC and IHBDMAC. Overall survival (OS) and cancer-specific survival (CSS) between the two pathological subtypes were compared. Univariate and multivariate Cox regression analyses were performed to identify potential and independent prognostic factors for OS in the entire cohort and in patients with IHBDMAC. Finally, propensity score matching (PSM) analysis was utilized to control for various factors significantly influencing OS, allowing for further investigation.

2.4. Statistical analysis

The software R version 4.2.2 was used for statistical analysis. The R package tableone was used for baseline comparison and subsequent table output. Categorical data were expressed as numbers (percentages). Categorical variables were evaluated *via* Chi-Squared and Fisher's

exact tests. Survival analyses were performed using the R packages survminer and survival. Kaplan–Meier curves and the corresponding risk tables were produced using the R command ggsurvplot. OS was defined as the time from the date of radical surgery to the date of death or last follow-up. The R packages survminer, dplyr, survival, and rms were used to construct a Cox proportional hazards model, which showed hazard ratios (HR) and their 95% confidence intervals (CI). P values lower than 0.05 indicated statistical significance. PSM analysis was performed using the R package MatchIt with the method="nearest," caliper=0.05, and ratio=1, matching factors that mainly consisted of age, sex, and other independent prognostic factors for OS.

3. Results

3.1. Comparative analysis of baseline characteristics

The baseline characteristics of the study population are summarized in Table 1. The cohort consisted of 1,126 patients, 1,083 of whom had IHBDAC and 43 of whom had IHBDMAC. The distribution of demographic and clinical variables, including age, sex, race, tumor grade, T stage, N stage, M stage, surgery status, radiotherapy, chemotherapy, CRD, marital status, AFP levels, and cirrhosis status, were compared between the two groups. Significant differences were noted in the T stage distribution (P = 0.012); patients with IHBDMAC more

Table 1. Baseline features before PSM

Variables	Overall (n = 1126)	IHBDAC (n = 1083)	IHBDMAC (n = 43)	P value
Age (%)				0.234
≤60	328 (29.1)	312 (28.8)	16 (37.2)	
>60	798 (70.9)	771 (71.2)	27 (62.8)	
Sex (%)				0.903
Male	592 (52.6)	569 (52.5)	23 (53.5)	
Female	534 (47.4)	514 (47.5)	20 (46.5)	
Race (%)				0.536
White	901 (80.0)	865 (79.9)	36 (83.7)	
Other	225 (20.0)	218 (20.1)	7 (16.3)	
Grade (%)				0.332
Well to moderately differentiated	311 (27.6)	297 (27.4)	14 (32.6)	
Poorly differentiated to undifferentiated	261 (23.2)	255 (23.5)	6 (14.0)	
Unknown	554 (49.2)	531 (49.0)	23 (53.5)	
T stage (%)				0.012
T1-T2	702 (62.3)	683 (63.1)	19 (44.2)	
T3-T4	424 (37.7)	400 (36.9)	24 (55.8)	
N stage (%)				0.070
N0	840 (74.6)	813 (75.1)	27 (62.8)	
N1	286 (25.4)	270 (24.9)	16 (37.2)	
M stage (%)				0.192
M0	782 (69.4)	756 (69.8)	26 (60.5)	
M1	344 (30.6)	327 (30.2)	17 (39.5)	
Surgery (%)				0.211
Not undergone	942 (83.7)	909 (83.9)	33 (76.7)	
Undergone	184 (16.3)	174 (16.1)	10 (23.3)	
Radiotherapy (%)				0.216
Not undergone	1086 (96.4)	1046 (96.6)	40 (93.0)	
Undergone	40 (3.6)	37 (3.4)	3 (7.0)	
Chemotherapy (%)				0.887
Not undergone	588 (52.2)	566 (52.3)	22 (51.2)	
Undergone	538 (47.8)	517 (47.7)	21 (48.8)	
CRD (%)				0.302
No	196 (17.4)	186 (17.2)	10 (23.3)	
Yes	930 (82.6)	897 (82.8)	33 (76.7)	
Marital status (%)				0.908
Single/unknown	514 (45.6)	494 (45.6)	20 (46.5)	
Married	612 (54.4)	589 (54.4)	23 (53.5)	
AFP (%)				0.958
Positive	345 (33.7)	331 (33.6)	14 (35.0)	
Negative	143 (14.0)	138 (14.0)	5 (12.5)	
No/unknown	537 (52.4)	516 (52.4)	21 (52.5)	
Cirrhosis (%)				0.055
No	45 (4.0)	42 (3.9)	3 (7.0)	
Yes	114 (10.1)	114 (10.5)	0 (0.0)	
No/unknown	967 (85.9)	927 (85.6)	40 (93.0)	

IHBDAC: intrahepatic bile duct adenocarcinoma; IHBDMAC: intrahepatic bile duct mucinous adenocarcinoma; CRD: cancer-related death; PSM: propensity score matching.

likely to present with an advanced T stage (T3-T4) (55.8% *vs.* 36.9%, $P = 0.012$). Moreover, lymph node metastasis was more frequently detected among patients with IHBDMAC (37.2% *vs.* 24.9%, $P = 0.070$).

3.2. Comparative analysis of survival outcomes

Kaplan-Meier survival curves revealed significant differences in OS and CSS between patients with IHBDAC and patients with IHBDMAC. Patients with IHBDMAC had a much worse OS (Figure 2A) and CSS (Figure 2B) than those with IHBDMAC ($P < 0.05$ for both).

3.3. Univariate and multivariate cox regression analysis

Univariate and multivariate cox regression analyses were performed to identify prognostic factors for the entire cohort (Table 2) and specifically for patients with IHBDMAC (Table 3). For the entire cohort, as is summarized in Table 2, age, tumor differentiation grade, T stage, N stage, M stage, chemotherapy, radiotherapy, and surgery status were found to be prognostic factors in univariate analyses. In multivariate analyses, patients over the age of 60 had a significantly higher risk of mortality (HR = 1.270, 95% CI: 1.109-1.454, $P = 0.001$). Poorly differentiated to undifferentiated tumors were associated with worse outcomes (HR = 1.420, 95% CI: 1.198-1.683, $P < 0.001$). An advanced T stage (T3-T4) was a significant predictor of poor survival (HR = 1.417, 95% CI: 1.244-1.615, $P < 0.001$). Positive nodal status (N1) was also associated with worse survival (HR = 1.283, 95% CI: 1.109-1.485, $P = 0.001$). Distant metastasis (M1) significantly increased the mortality risk (HR = 1.477, 95% CI: 1.285-1.698, $P < 0.001$). Undergoing chemotherapy (HR = 0.576, 95% CI: 0.506-0.656, $P < 0.001$) and surgery (HR = 0.335, 95% CI: 0.277-0.405, $P < 0.001$) were protective factors for survival.

For patients with IHBDMAC, the M stage and surgery status were found to be prognostic factors in univariate analyses. In multivariate analyses, distant metastasis (M1) significantly increased the mortality risk in patients with IHBDMAC (HR = 2.427, 95% CI: 1.207-4.878, $P = 0.013$). Undergoing surgery was a protective factor for survival in patients with IHBDMAC (HR = 0.394, 95% CI: 0.178-0.874, $P = 0.022$).

3.4. Propensity score matching analysis

PSM analysis was performed account for confounding factors, resulting in 40 patients with IHBDAC matched to 40 patients with IHBDMAC. Post-matching baseline characteristics (Table 4) revealed no significant differences in key variables, ensuring balanced groups for comparison. Post-PSM survival analysis confirmed that IHBDMAC was still associated with a worse OS (Figure 3A) and CSS (Figure 3B) compared to IHBDAC.

4. Discussion

The prognostic value of mucinous components has been explored in patients with various solid tumors, including colon cancer (*6*), rectal cancer (*7*), ovary cancer (*8*), and pulmonary cancer (*9*). These studies consistently indicated that the mucinous component was associated with a more aggressive tumor biological features, reduced response to chemotherapy, and worse prognosis. However, in patients with IHCC, the differences in clinicopathological factors and long-term prognosis brought about by the mucinous component compared

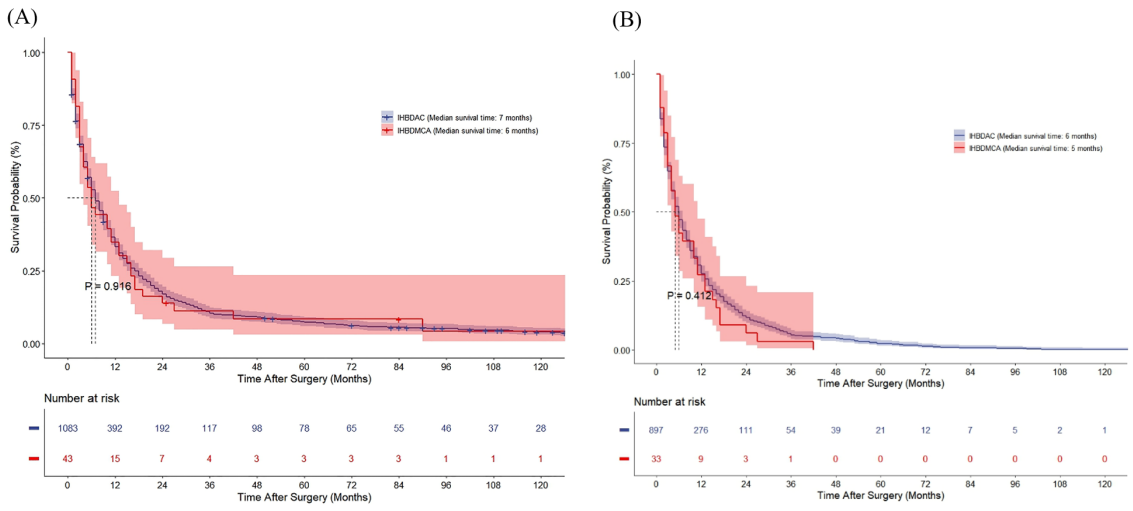

Figure 2. KM curves showing survival differences between patients with IHBDAC and patients with IHBDMAC. A, OS; B, CSS. IHBDAC: intrahepatic bile duct adenocarcinoma carcinoma; IHBDMAC: intrahepatic bile duct mucinous adenocarcinoma. OS: overall survival; CSS: cancer-specific survival.

Table 2. Univariate and multivariate Cox regression of the entire cohort

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
≤60				
>60	1.209 (1.058,1.382)	0.005	1.270 (1.109,1.454)	0.001
Sex				
Male				
Female	0.910 (0.807,1.026)	0.122		
Race				
White				
Other	0.956 (0.821,1.114)	0.566		
Grade				
Well to moderately differentiated				
Poorly differentiated to undifferentiated	1.477 (1.247,1.749)	< 0.001	1.420 (1.198,1.683)	< 0.001
Unknown	1.321 (1.144,1.524)	< 0.001	1.075 (0.929,1.244)	0.334
AFP				
Positive				
Negative	0.893 (0.730,1.091)	0.267		
No/unknown	1.021 (0.889,1.172)	0.770		
Marital status				
Single/unknown				
Married	0.957 (0.849,1.079)	0.474		
Pathology				
IHBDAC				
IHBDMAC	1.015 (0.740,1.393)	0.925		
Cirrhosis				
No				
Yes	1.242 (0.871,1.771)	0.232		
No/unknown	1.248 (0.916,1.700)	0.161		
T stage				
T1-T2				
T3-T4	1.532 (1.352,1.737)	< 0.001	1.417 (1.244,1.615)	< 0.001
N stage				
N0				
N1	1.375 (1.199,1.576)	< 0.001	1.283 (1.109,1.485)	0.001
M stage				
M0				
M1	1.621 (1.422,1.847)	< 0.001	1.477 (1.285,1.698)	< 0.001
Chemotherapy				
Not undergone				
Undergone	0.799 (0.708,0.901)	< 0.001	0.576 (0.506,0.656)	< 0.001
Radiotherapy				
Not undergone				
Undergone	0.520 (0.373,0.725)	< 0.001	1.086 (0.764,1.545)	0.644
Surgery				
Not undergone				
Undergone	0.334 (0.280,0.398)	< 0.001	0.335 (0.277,0.405)	< 0.001

HR: hazard ratio; CI: confidence interval; IHBDAC: intrahepatic bile duct adenocarcinoma; IHBDMAC: intrahepatic bile duct mucinous adenocarcinoma.

to conventional IHCC have not yet been systematically explored. Consequently, the current study represents the first systematic evaluation of the clinical and pathological features and survival outcomes of patients with IHBDAC and IHBDMAC. Through meticulous data collection and analysis, several key insights have been gained, shedding light on the distinct characteristics and prognostic factors associated with these two subtypes of IHCC.

The baseline characteristics of the cohort revealed that patients with IHBDMAC tend to have a more advanced T stage compared to those with IHBDAC. This finding suggests a potentially more aggressive disease course in IHBDMAC, which is further supported by the survival analyses showing a significantly worse OS and CSS in patients with IHBDMAC. These findings were consistent with observations as mentioned earlier (*6-9*). This aggressive behavior of IHBDMAC could be attributed to the unique biological and molecular properties of mucinous tumors, which are known to exhibit higher invasiveness and metastatic potential. Using single-cell profiling, researchers have indicated that mucinous adenocarcinoma cancer cells exhibit goblet cell-like properties and express high levels of goblet cell markers (REG4, SPINK4, FCGBP, and

Table 3. Univariate and multivariate Cox regression of patients with IHBDMAC

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age				
≤60				
>60	2.025 (1.038,3.953)	0.039	1.718 (0.855,3.452)	0.129
Sex				
Male				
Female	0.843 (0.447,1.592)	0.599		
Race				
White				
Other	0.466 (0.181,1.198)	0.113		
Grade				
Well to moderately differentiated				
Poorly differentiated to undifferentiated	0.943 (0.357,2.491)	0.905		
Unknown	0.650 (0.323,1.309)	0.228		
AFP				
Positive				
Negative	0.967 (0.310,3.017)	0.954		
No/unknown	1.182 (0.580,2.411)	0.645		
Marital status				
Single/unknown				
Married	1.045 (0.559,1.953)	0.891		
Cirrhosis				
No				
No/unknown	2.095 (0.502,8.742)	0.310		
T stage				
T1-T2				
T3-T4	1.120 (0.598,2.099)	0.723		
N stage				
N0				
N1	1.285 (0.675,2.448)	0.446		
M stage				
M0				
M1	2.766 (1.396,5.480)	0.004	2.427 (1.207,4.878)	0.013
Chemotherapy				
Not undergone				
Undergone	1.219 (0.648,2.295)	0.539		
Radiotherapy				
Not undergone				
Undergone	0.504 (0.153,1.660)	0.260		
Surgery				
Not undergone				
Undergone	0.338 (0.157,0.728)	0.006	0.394 (0.178,0.874)	0.022

HR: hazard ratio; CI: confidence interval; IHBDMAC: intrahepatic bile duct mucinous adenocarcinoma.

MUC2) compared to classical adenocarcinoma cancer cells. TFF3 is essential for the transcriptional regulation of these molecules and may cooperate with RPS4X to ultimately lead to the mucinous adenocarcinoma mucus phenotype (*10*). Moreover, Kaplan-Meier survival curves showed that patients with IHBDMAC have markedly poorer survival outcomes compared to those with IHBDAC, both before and after PSM. The persistence of significant survival differences post-PSM indicates that the worse prognosis associated with IHBDMAC is intrinsic to the tumor biology rather than due to differences in patient demographics or treatment modalities. This underscores the need for tailored therapeutic strategies for patients with IHBDMAC to improve their survival outcomes. In addition, the Cox regression analyses identified several prognostic factors for the entire cohort and for IHBDMAC specifically. For the entire cohort, age, tumor grade, T stage, N stage, M stage, chemotherapy, and surgery were significant predictors of survival. Notably, age and advanced T stage were associated with increased mortality while chemotherapy and surgical interventions were protective factors. This aligns with existing literature emphasizing the importance of early detection and aggressive treatment in improving outcomes for patients with IHCC. In the IHBDMAC subgroup, metastatic status (M1) emerged as a significant adverse prognostic factor, whereas surgical resection was associated with improved survival. The pronounced impact of metastasis on survival in patients with IHBDMAC highlights the critical need for effective systemic therapies to manage distant disease spread. Moreover, the benefit of surgery

Table 4. Baseline features after PSM

Variables	Overall (*n* = 80)	IHBDAC (*n* = 40)	IHBDMAC (*n* = 40)	*P* value
Age (%)				1.000
≤60	28 (35.0)	14 (35.0)	14 (35.0)	
>60	52 (65.0)	26 (65.0)	26 (65.0)	
Sex (%)				0.654
Male	42 (52.5)	20 (50.0)	22 (55.0)	
Female	38 (47.5)	20 (50.0)	18 (45.0)	
Race (%)				0.108
White	62 (77.5)	28 (70.0)	34 (85.0)	
Other	18 (22.5)	12 (30.0)	6 (15.0)	
Grade (%)				1.000
Well to moderately differentiated	24 (30.0)	12 (30.0)	12 (30.0)	
Poorly differentiated to undifferentiated	10 (12.5)	5 (12.5)	5 (12.5)	
Unknown	46 (57.5)	23 (57.5)	23 (57.5)	
T stage (%)				1.000
T1-T2	38 (47.5)	19 (47.5)	19 (47.5)	
T3-T4	42 (52.5)	21 (52.5)	21 (52.5)	
N stage (%)				1.000
N0	54 (67.5)	27 (67.5)	27 (67.5)	
N1	26 (32.5)	13 (32.5)	13 (32.5)	
M stage (%)				1.000
M0	48 (60.0)	24 (60.0)	24 (60.0)	
M1	32 (40.0)	16 (40.0)	16 (40.0)	
Surgery (%)				1.000
Not undergone	64 (80.0)	32 (80.0)	32 (80.0)	
Undergone	16 (20.0)	8 (20.0)	8 (20.0)	
Radiotherapy (%)				0.556
Not undergone	77 (96.2)	39 (97.5)	38 (95.0)	
Undergone	3 (3.8)	1 (2.5)	2 (5.0)	
Chemotherapy (%)				1.000
Not undergone	42 (52.5)	21 (52.5)	21 (52.5)	
Undergone	38 (47.5)	19 (47.5)	19 (47.5)	
CRD (%)				0.793
No	19 (23.8)	9 (22.5)	10 (25.0)	
Yes	61 (76.2)	31 (77.5)	30 (75.0)	
Marital status (%)				0.501
Single/unknown	43 (53.8)	23 (57.5)	20 (50.0)	
Married	37 (46.2)	17 (42.5)	20 (50.0)	
AFP (%)				0.873
Positive	26 (35.1)	12 (32.4)	14 (37.8)	
Negative	11 (14.9)	6 (16.2)	5 (13.5)	
No/unknown	37 (50.0)	19 (51.4)	18 (48.6)	
Cirrhosis (%)				0.038
No	4 (5.0)	2 (5.0)	2 (5.0)	
Yes	6 (7.5)	6 (15.0)	0 (0.0)	
No/unknown	70 (87.5)	32 (80.0)	38 (95.0)	

IHBDAC: intrahepatic bile duct adenocarcinoma; IHBDMAC: intrahepatic bile duct mucinous adenocarcinoma; CRD: cancer-related death; PSM: propensity score matching.

underscores the importance of considering surgical options even in advanced stages, provided the patient's condition permits.

The current findings have several important implications for clinical practice. First, the distinct survival outcomes between IHBDAC and IHBDMAC necessitate a differential approach to diagnosis, treatment, and management. Given the poorer prognosis of IHBDMAC, clinicians should remain highly suspicious of aggressive disease and consider comprehensive staging and early systemic therapy to manage potential metastases. Second, the identification of key prognostic factors such as tumor grade, T stage, and metastatic status can aid in stratifying patients based on their risk profiles. This stratification can inform treatment decisions, enabling a more personalized approach to patient care. For instance, patients with high-risk features may benefit from more intensive monitoring and adjuvant therapies to address micro-metastatic disease and improve survival outcomes. Third, in the latest version of the AJCC staging system, pathological subtype is not considered a prognostic factor for IHCC. However, based on our research and previous studies, we believe that pathological subtype should also be regarded as a key prognostic factor for IHCC. In addition, more comprehensive and precise prognostic models for IHCC

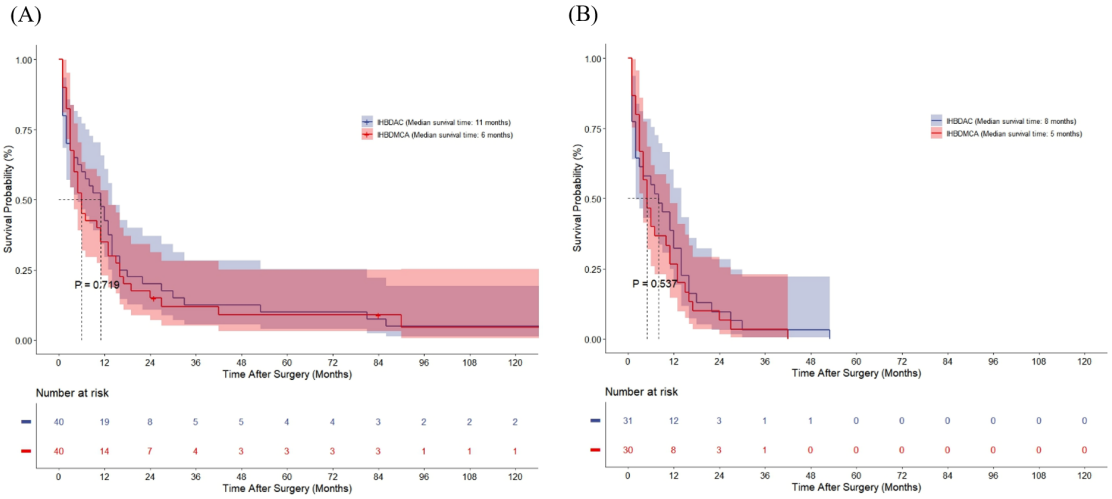

Figure 3. KM curves showing survival differences between patients with IHBDAC and patients with IHBDMAC after matching. A, OS; B, CSS. IHBDAC: intrahepatic bile duct adenocarcinoma carcinoma; IHBDMAC: intrahepatic bile duct mucinous adenocarcinoma. OS: overall survival; CSS: cancer-specific survival.

should be developed in larger clinical cohorts in the future, incorporating pathological subtype and other reported factors.

Despite the strengths of this study, including a robust sample size and thorough statistical analysis, several limitations warrant consideration. The retrospective nature of this study may introduce selection bias, and the reliance on registry data means that certain clinical details, such as comorbidities and detailed treatment regimens, were not available. In addition, the relatively small number of patients with IHBDMAC might limit the generalizability of findings to all mucinous adenocarcinomas of the intrahepatic bile ducts. In addition, mucinous colorectal adenocarcinoma is a distinct subtype of colorectal cancer that is characterized by the presence of abundant extracellular mucin, which accounts for at least 50% of the tumor volume (*6*). However, the specific definition of IHBDMAC has not yet been clarified, particularly regarding the optimal cut-off value for the mucinous component when defining IHBDMAC. Future research should focus on prospective studies with larger cohorts to validate our findings and explore the underlying molecular mechanisms driving the aggressive behavior of IHBDMAC. Understanding the genetic and epigenetic alterations specific to mucinous tumors could reveal novel therapeutic targets and lead to the development of more effective treatment strategies.

In conclusion, the current study has highlighted significant differences in the clinical and pathological characteristics and survival outcomes of IHBDAC and IHBDMAC. Patients with IHBDMAC have a worse prognosis, driven by more advanced disease at presentation and a higher metastatic potential. Key prognostic factors identified in our analysis, such as tumor grade, T stage, and metastatic status, can guide risk stratification and personalized treatment approaches. Surgical resection remains a critical component of the management strategy, even in advanced cases, and systemic therapies are crucial to controlling metastatic disease. Future research should aim to elucidate the molecular underpinnings of IHBDMAC to develop targeted therapies that can improve survival outcomes for this challenging subtype of intrahepatic cholangiocarcinoma.

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