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ORIGINAL ARTICLE

Retrospective Study

# Prognostic significance of germline *ARID5B* and *LEPR* polymorphisms in intrahepatic and perihilar cholangiocarcinoma after curative resection

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## Abstract

***BACKGROUND***

Cholangiocarcinoma (CCA) is a biologically heterogeneous and aggressive biliary malignancy associated with poor survival outcomes despite surgical resection. Germline genetic variants, including single-nucleotide polymorphisms (SNPs), may modulate tumor behavior and inform postoperative risk stratification.

***AIM***

To evaluate the prognostic relevance of selected tumor-related SNPs in patients with intrahepatic CCA (iCCA) and perihilar CCA (pCCA).

***METHODS***

In this single-centre retrospective cohort study, we genotyped eight SNPs in cancer-associated genes (*ARID5B*, *LEPR*, *TERT*, *SH2B3*, *MMEL1*, *PROM1*, *HDAC7*, *RUNX3*) in 229 patients (112 iCCA, 117 pCCA) who underwent curative-intent resection between 2009 and 2020.

***RESULTS***

Associations between SNPs and recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were assessed using Kaplan-Meier analysis, univariate, and multivariate Cox regression models. The rs10740055 AA genotype in *ARID5B* was associated with significantly shorter RFS [hazard ratio (HR) = 1.87, $P$ = 0.017], CSS (HR = 1.78, $P$ = 0.033) and OS (HR = 1.79, $P$ = 0.021) in iCCA as well as shorter RFS (HR = 1.84, $P$ = 0.031), CSS (HR = 2.18, $P$ = 0.005) and OS (HR = 1.84, $P$ = 0.001) univariate analyses. However, only in iCCA did it retain significance in multivariate analysis alongside other important clinicopathological variables (RFS: HR = 2.41, $P$ = 0.005; CSS: HR = 2.27, $P$ = 0.020 and OS: HR = 4.10, $P$ = 0.001). Further, the *LEPR* rs1137101 GG genotype was associated with significantly shorter RFS (HR = 1.91, $P$ = 0.010). Germline variants in *ARID5B* and *LEPR* were associated with poorer prognosis following resection for CCA, with rs10740055 in *ARID5B* serving as an independent predictor of survival particularly in iCCA.

***CONCLUSION***

These findings support the potential utility of incorporating host genetic markers into postoperative prognostic models for CCA. Prospective validation and mechanistic studies are warranted.

**Key Words:** Cholangiocarcinoma; Single-nucleotide polymorphisms; *ARID5B*; *LEPR*; Prognostic biomarker

**Core Tip:** This study identifies germline *ARID5B* rs10740055 and *LEPR* rs1137101 polymorphisms as prognostic biomarkers in patients undergoing curative resection for intrahepatic and perihilar cholangiocarcinoma. In a cohort of 229 patients, the *ARID5B* rs10740055 AA genotype was consistently associated with significantly worse recurrence-free, cancer-specific, and overall survival, serving as an independent predictor particularly in intrahepatic cholangiocarcinoma. The *LEPR* rs1137101 GG genotype was additionally associated with shorter recurrence-free survival in intrahepatic tumors. These findings highlight the potential value of incorporating host genetic variants into postoperative risk stratification and personalized management strategies for cholangiocarcinoma.

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## INTRODUCTION

Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary tract, classified anatomically as intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA[1,2]. Even after curative-intent resection, recurrence rates remain high, and overall prognosis continues to be unsatisfactory compared to other solid cancers[3-5]. Thus, identifying novel prognostic biomarkers is urgently needed to facilitate patient stratification and personalized therapeutic approaches[6].

Recent research has increasingly focused on genetic susceptibility factors associated with CCA prognosis. Single-nucleotide polymorphisms (SNPs), in particular, have emerged as potential genetic markers that may influence tumor progression and patient outcomes[7]. Several studies have demonstrated associations between specific SNPs and CCA prognosis. For example, *IDH1*$^{105GGT}$ SNP is associated with its activation and better prognosis in iCCA[8]. Similarly, the rs887569 TT genotype was correlated with a significantly longer overall survival (OS) in CCA[9]. These findings underscore a growing trend towards the identification of genetic polymorphisms as potential biomarkers for prognostic prediction and clinical decision-making in CCA.

In this context, we selected a set of SNPs in genes implicated in cancer pathogenesis, including rs10740055 and rs1137101, to investigate their potential prognostic value in CCA. The selected genes span critical oncogenic pathways, encompassing cell proliferation and tumor suppression (*e.g.*, *ARID5B*, *RUNX3*), genomic stability and cellular immortalisation (*TERT*), invasion and metastasis (*PROM1*), metabolic and inflammatory signaling (*LEPR*, *SH2B3*/*MMEL1*), and epigenetic regulation (*HDAC7*). A more detailed overview of the selected SNPs and their biological rationale is presented in Supplementary Table 1.

Based on this rationale, we aimed to evaluate associations between these tumor-related SNPs and patient outcomes in both iCCA and pCCA cohorts. By covering major anatomical subtypes of CCA, our study seeks to identify prognostic biomarkers that are relevant across these subtypes, thereby improving understanding of molecular heterogeneity and facilitating individualized prognostic assessments.

## MATERIALS AND METHODS

### Study population

We retrospectively analyzed patients who underwent curative-intent resection for iCCA or pCCA at RWTH Aachen University Hospital between May 2009 and December 2020. After excluding perioperative mortality, a total of 229 patients (112 iCCA, 117 pCCA) were included. Ethical approval was granted by the Institutional Review Board of RWTH Aachen University (No. EK 252/15; No. EK 206/09), and the study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Given the single-center design and the relatively homogeneous patient population, population stratification was considered unlikely to substantially affect the observed genotype distributions.

### DNA extraction and quantification

DNA extraction was carried out as previously described[6]. In brief, non-tumor tissue samples were obtained from formalin-fixed, paraffin-embedded (FFPE) liver specimens after evaluation by a pathologist. DNA isolation was performed using the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) as previously described[6]. DNA quality and concentration were assessed spectrophotometrically, and only samples with adequate purity (A260/280 ratio 1.8-2.0) and yield (> 10 ng/μL) were included. Extracted DNA was stored at -20 °C until genotyping.

### SNP selection

We systematically selected SNPs involved in critical oncogenic pathways based on defined criteria: (1) Documented polymorphisms with plausible biological relevance; (2) Sufficient frequency to enable statistically meaningful analysis; and (3) Previously unexplored associations with CCA prognosis in existing literature. Following these guidelines, eight SNPs from eight candidate genes were selected. The selected SNPs were prioritized based on a combination of biological plausibility and previously reported associations with cancer-related pathways. Specifically, variants were chosen if they fulfilled at least one of the following criteria: (1) Evidence of functional relevance affecting gene regulation or protein function; (2) Prior associations with cancer susceptibility or tumor biology in genome-wide association or candidate gene studies; or (3) Involvement of the corresponding gene in pathways known to contribute to tumor development, including proliferation, immune signaling, epigenetic regulation, and cancer stem cell biology. Although most of these polymorphisms have been investigated in other malignancies, their prognostic relevance in CCA has not been systematically explored to date. A detailed overview of the investigated SNPs, their biological functions, and related oncogenic pathways is provided in Supplementary Table 1. In this study, the following SNPs were included: *ARID5B* rs10740055, *HDAC7* rs11168249, *LEPR* rs1137101, *TERT* rs2736100, *SH2B3* rs3184504, *PROM1* rs3130, *MMEL1* rs3748816, and *RUNX3* rs7528484. Comprehensive details are provided in Supplementary Table 1.

### SNP analysis

Genotyping was performed using TaqMan assays (Thermo Fisher Scientific, CA, United States) on the ABI 7500 real-time polymerase chain reaction platform, following the manufacturer's instructions. Overall genotype call rates exceeded 95% for all analyzed SNPs. Positive and negative controls were included in each genotyping run. Reaction conditions and quality control procedures were identical to those described previously[6]. Allelic discrimination was performed using VIC and FAM fluorescent probes, with positive/negative controls included in each run. Samples with insufficient DNA quality or ambiguous genotype calls were excluded prior to statistical analysis. Comprehensive details are provided in Supplementary Table 1.

### Statistical analysis

Hardy-Weinberg equilibrium (HWE) was tested for each SNP using Pearson's $\chi^2$. SNPs showing significant deviation from HWE were excluded from further analyses. Prognostic endpoints were recurrence-free survival (RFS), cancer-

specific survival (CSS), and OS, calculated from the date of surgery. Statistical analyses were conducted as previously[9]. Due to the retrospective design and the rarity of CCA, a formal a priori power calculation was not feasible. Briefly, categorical variables were compared with Fisher's exact test, continuous variables with Mann-Whitney *U* or Kruskal-Wallis tests, and survival distributions with Kaplan-Meier and log-rank methods. Cox proportional hazards (PH) regression was applied for univariate and multivariable analyses. Variables with $P < 0.1$ in univariate testing were entered into multivariable models. Significance was set at $P < 0.05$. Missing data were handled using complete-case analysis. No imputation was performed. For each analysis, patients with missing values in the corresponding variables were excluded. To assess model robustness, events per variable (EPV) were calculated for all multivariable Cox models, and additional sensitivity analyses using reduced models were performed. The PH assumption for all Cox regression models was formally assessed by examining correlations between partial (scaled Schoenfeld-type) residuals and ranked survival time. A significant correlation was interpreted as potential evidence of time-dependent effects. Analyses were performed using SPSS Statistics (version 26.0, IBM, Armonk, NY, United States).

## RESULTS

### *ICCA*

Among 112 patients with iCCA, median age was 65 years, and 56.3% were female. Most patients were categorized as American Society of Anesthesiologists classification II or III. Right or left hepatectomy were the most frequent procedures (39.2%), with an R0 resection rate of 86.6%. Median RFS, CSS and OS were 12 months, 28 months, and 25 months, respectively (Table 1).

Eight SNPs were genotyped. All SNPs met HWE with the exception of rs3184504 (*SH2B3*) and rs3130 (*PROM1*). Missing genotype data for iCCA were as follows: Rs10740055 ($n = 1$), rs11168249 ($n = 1$), rs2736100 ($n = 8$), rs3130 ($n = 14$). Detailed genotype distributions are shown in Supplementary Tables 2 and 3.

Univariate Cox regression showed that hemoglobin > 12 g/dL was associated with improved RFS [hazard ratio (HR) = 0.582, 95% confidence interval (CI): 0.341-0.995, $P = 0.048$], CSS (HR = 0.471, 95%CI: 0.270-0.823, $P = 0.008$), and OS (HR = 0.454, 95%CI: 0.270-0.762, $P = 0.003$). Conversely, elevated C-reactive protein, gamma-glutamyl transpeptidase, alkaline phosphatase, microvascular invasion (MVI), lymphovascular invasion (LVI), advanced Union for International Cancer Control stage, lymph-node metastasis (pN1), and Clavien-Dindo ≥ III complications were consistently associated with poorer outcomes (all $P < 0.05$) (Supplementary Table 4).

Kaplan-Meier and Cox analyses revealed significant associations between SNPs and prognosis. Under the recessive genetic model (AA *vs* CC/CA), rs10740055 (*ARID5B*) was associated with shorter RFS (Kaplan-Meier $P = 0.013$; HR = 1.866, 95%CI: 1.116-3.121, Cox $P = 0.017$), CSS (Kaplan-Meier $P = 0.029$; HR = 1.776, 95%CI: 1.046-3.015, Cox $P = 0.033$), and OS (Kaplan-Meier $P = 0.018$; HR = 1.791, 95%CI: 1.093-2.932, Cox $P = 0.021$). Additionally, rs1137101 GG genotype was associated with shorter RFS (Kaplan-Meier $P = 0.007$; HR = 1.910, 95%CI: 1.170-3.116, Cox $P = 0.010$). No other SNPs reached significance (Figure 1 and Table 2).

Multivariable Cox regression confirmed rs10740055 AA genotype as an independent predictor for poorer RFS (HR = 2.413, 95%CI: 1.311-4.440, $P = 0.005$), CSS (HR = 2.265, 95%CI: 1.137-4.513, $P = 0.020$), and OS (HR = 4.095, 95%CI: 1.966-8.529, $P < 0.001$). Other independent predictors were neoadjuvant therapy (RFS), low hemoglobin (CSS and OS), LVI (RFS and OS), and lymph-node metastasis (CSS) (Table 3). The PH assumption was formally assessed for all multivariable Cox models using correlation analyses between partial residuals and ranked survival time (Supplementary Table 5). In the iCCA cohort, the PH assumption was fulfilled for all covariates in the RFS and OS models. In the CSS model, a mild deviation was observed for lymph node status (N1) ($r = -0.261$, $P = 0.037$). However, the magnitude of correlation was moderate, and visual inspection did not suggest clinically meaningful time-dependent effects. Importantly, no violation of the PH assumption was observed for the primary genetic variable rs10740055 in any model.

In the iCCA cohort, EPV values indicated excellent model stability (EPV 21.3-25.0; Supplementary Table 6), and reduced-model sensitivity analyses confirmed robust and consistent effect estimates for the key predictors (*e.g.*, rs10740055 and LVI) across RFS, CSS, and OS (Supplementary Table 7).

### *PCCA*

In 117 patients with pCCA, median age was 69 years, and 66.7% were male. Cholangitis was reported in 25.6% of patients, and 35.0% underwent portal-vein embolization. Extended hepatectomy was most common (46.2%), achieving R0 resection in 82.9% of cases. Median RFS, CSS, and OS were 37 months, 49 months, and 33 months, respectively (Table 1).

All tested SNPs met HWE except for rs11168249 (*HDAC7*) and rs2736100. Missing SNP data for pCCA were as follows: Rs11168249 ($n = 1$), rs2736100 ($n = 9$), rs3130 ($n = 12$). Genotype distributions are summarized in Supplementary Table 8. Univariate analysis identified hemoglobin ≤ 12 g/dL, intraoperative transfusion [packed red blood cells or fresh frozen plasma (FFP)], MVI, poor tumor differentiation (G3/G4), advanced T (pT3-4) and N (pN1) stages, and severe postoperative complications (Clavien-Dindo ≥ III) as adverse prognostic indicators (all $P < 0.05$) (Supplementary Table 9).

Kaplan-Meier analysis demonstrated that the rs10740055 AA genotype was associated with significantly shorter RFS, CSS, and OS in patients with pCCA. These findings were confirmed by univariate Cox regression analyses, showing increased hazards for RFS (HR = 1.840), CSS (HR = 2.184), and OS (HR = 1.840). Under the co-dominant model, the AA genotype also predicted poorer CSS (HR = 2.070, 95%CI: 1.077-3.977, Cox $P = 0.029$) and OS (HR = 2.467, 95%CI: 1.392-4.373, Cox $P = 0.002$). Other SNPs were not significantly associated with outcomes (Table 4).

**Table 1 Patient characteristics, *n* (%)/median and interquartile range**

| Variables | iCCA (*n* = 112) | pCCA (*n* = 117) |
|---|---|---|
| Demographics | | |
| Gender, M/F (%) | 49 (43.8)/63 (56.3) | 78 (66.7)/39 (33.3) |
| Age (years) | 65 (58-75) | 69 (58-74) |
| ASA | | |
| I | 3 (2.7) | 6 (5.1) |
| II | 45 (40.2) | 47 (40.2) |
| III | 59 (52.7) | 58 (49.6) |
| IV | 5 (4.5) | 6 (5.1) |
| V | 0 | 0 |
| Bismuth type | | |
| I | | 7 (6.0) |
| II | | 13 (11.1) |
| IIIa | | 29 (24.8) |
| IIIb | | 33 (28.2) |
| IV | | 35 (29.9) |
| Cholangitis | 4 (3.6) | 30 (25.6) |
| Portal vein embolization | 7 (6.3) | 41 (35.0) |
| Preoperative chemotherapy | 9 (8.0) | 5 (4.3) |
| Clinical chemistry | | |
| AST (U/L) | 34 (26-47) | 47 (34-95) |
| ALT (U/L) | 29 (20-49) | 69 (36-144) |
| Albumin (g/dL) | 4.4 (4.0-4.6) | 3.9 (3.5-4.2) |
| AP (U/L) | 118 (84-215) | 254 (159-423) |
| CA19-9 (U/mL) | 39.5 (13.9-236.3) | 85.8 (31.2-287.7) |
| CRP (mg/L) | 7.5 (2.8-19.4) | 11.8 (5.4-34.7) |
| GGT (U/L) | 113 (65-275) | 472 (216-756) |
| Hemoglobin (g/dL) | 13.1 (12.2-14.3) | 12.4 (11.2-13.3) |
| INR | 1.0 (0.9-1.1) | 1.0 (0.9-1.1) |
| Platelet count (nL) | 252 (202-306) | 293 (229-388) |
| Prothrombin time (%) | 100 (90-108) | 96 (81-105) |
| Total bilirubin (mg/dL) | 0.5 (0.3-0.7) | 1.1 (0.5-2.8) |
| Operative data | | |
| Intraoperative PRBC | 31 (72.3) | 54 (46.2) |
| Intraoperative FFP | 38 (33.9) | 68 (58.1) |
| Operative time (minutes) | 295 (230-359) | 420 (356-485) |
| Operative procedure | | |
| Hemihepatectomy | 44 (39.2) | 29 (24.8) |
| Extended hemihepatectomy | 17 (15.1) | 54 (46.2) |
| Trisectionectomy | 12 (10.8) | 24 (20.6) |
| Hepatoduodenoectomy | 0 (0) | 5 (4.3) |
| ALPPS | 10 (8.9) | 1 (0.9) |

| | | |
|---|---|---|
| Others | 29 (25.8) | 4 (3.4) |
| Time to surgery (days[1]) | 45 (29-83) | 38 (24-56) |
| Pathological examination | | |
| LVI | 20 (17.9) | 26 (22.2) |
| MVI | 5 (4.5) | 2 (1.7) |
| R0 resection | 97 (86.6) | 97 (82.9) |
| pT category | | |
| 1 | 46 (41.1) | 10 (8.6) |
| 2 | 46 (41.1) | 72 (61.5) |
| 3 | 12 (10.7) | 26 (22.2) |
| 4 | 8 (7.1) | 9 (7.7) |
| pN category | | |
| N0 | 69 (61.6) | 67 (57.3) |
| N1 | 34 (30.4) | 50 (42.7) |
| Tumor grading | | |
| G1 | 0 | 7 (6.0) |
| G2 | 73 (65.2) | 83 (70.9) |
| G3 | 26 (23.2) | 22 (18.8) |
| G4 | 3 (2.7) | 1 (0.9) |
| Postoperative data | | |
| Intensive care (days) | 1 (1-1) | 1 (1-2) |
| Hospitalization (days) | 12 (8-22) | 17 (12-36) |
| Postoperative complications | | |
| No complications | 43 (38.4) | 19 (16.2) |
| Clavien-Dindo I | 4 (3.6) | 8 (6.8) |
| Clavien-Dindo II | 24 (21.4) | 33 (28.2) |
| Clavien-Dindo IIIa | 25 (22.3) | 25 (28.2) |
| Clavien-Dindo IIIb | 10 (8.9) | 19 (16.2) |
| Clavien-Dindo IVa | 5 (4.5) | 8 (6.8) |
| Clavien-Dindo IVb | 1 (0.9) | 5 (4.3) |
| Clavien-Dindo V | 0 | 0 |
| Oncologic data | | |
| Adjuvant chemotherapy | 42 (37.5) | 31 (26.5) |
| Recurrence | 77 (68.8) | 64 (54.7) |
| Median RFS, months (95%CI) | 12 (7-17) | 37 (23-51) |
| Median CSS, months (95%CI) | 28 (21-35) | 49 (24-74) |
| Median OS, months (95%CI) | 25 (18-32) | 33 (20-46) |

[1]Time to surgery refers to the time frame from diagnosis to surgery.

iCCA: Intrahepatic cholangiocarcinoma; pCCA: Perihilar cholangiocarcinoma; M: Male; F: Female; AP: Alkaline Phosphatase; ASA: American Society of Anesthesiology; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CA19-9: Carbohydrate antigen 19-9; CRP: C-reactive protein; GGT: Gamma-glutamyl transpeptidase; INR: International normalized ratio; PRBC: Packed red blood cells; FFP: Fresh frozen plasma; ALPPS: Associating liver partition with portal vein ligation for staged hepatectomy; LVI: Lymph vascular invasion; MVI: Microvascular invasion; CSS: Cancer-specific survival; OS: Overall Survival; RFS: Recurrence free survival.

**Table 2 Single nucleotide polymorphism frequencies and associations with recurrence-free survival, cancer-specific survival and overall survival in intrahepatic cholangiocarcinoma**

| SNP | *n* (%) | Recurrence-free survival | | | | Cancer-specific survival | | | | Overall survival | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Median (95%CI) | *P* value[1] | HR (95%CI) | *P* value[2] | Median (95%CI) | *P* value[1] | HR (95%CI) | *P* value[2] | Median (95%CI) | *P* value[1] | HR (95%CI) | *P* value[2] |
| Recessive model | | | | | | | | | | | | | |
| rs10740055 | | | 0.013 | | | | 0.029 | | | | 0.018 | | |
| CC/CA | 85 (75.9) | 13 (8.7-17.1) | | 1 | | 30 (18.3-41.7) | | 1 | | 28 (21.0-35.0) | | 1 | |
| AA | 26 (23.2) | 8 (3.9-12.1) | | 1.866 (1.116-3.121) | 0.017 | 16 (8.3-26.7) | | 1.776 (1.046-3.015) | 0.033 | 12 (3.0-21.0) | | 1.791 (1.093-2.932) | 0.021 |
| rs11168249 | | | 0.125 | | | | 0.662 | | | | 0.332 | | |
| TT/TC | 94 (84.0) | 13 (8.3-17.7) | | 1 | | 28 (15.4-40.6) | | 1 | | 25 (17.5-32.5) | | 1 | |
| CC | 18 (16.1) | 7 (4.6-9.4) | | 1.602 (0.861-2.982) | 0.137 | 31 (17.5-44.5) | | 1.154 (0.603-2.208) | 0.665 | 24 (9.4-38.6) | | 1.328 (0.742-2.378) | 0.339 |
| rs1137101 | | | 0.007 | | | | 0.107 | | | | 0.221 | | |
| AA/AG | 83 (74.1) | 16 (10.3-21.7) | | 1 | | 36 (21.7-50.3) | | 1 | | 29 (15.9-42.1) | | 1 | |
| GG | 29 (25.9) | 7 (6.2-7.8) | | 1.910 (1.170-3.116) | 0.010 | 20 (12.2-27.8) | | 1.506 (0.907-2.500) | 0.113 | 20 (13.0-27.0) | | 1.342 (0.833-2.164) | 0.227 |
| rs2736100 | | | 0.879 | | | | 0.782 | | | | 0.610 | | |
| CC/CA | 75 (67.0) | 13 (7.0-19.0) | | 1 | | 30 (19.2-40.8) | | 1 | | 28 (17.3-38.7) | | 1 | |
| AA | 29 (25.9) | 11 (5.6-16.4) | | 1.043 (0.610-1.781) | 0.878 | 29 (10.0-47.9) | | 0.922 (0.517-1.646) | 0.784 | 20 (9.4-30.5) | | 1.139 (0.687-1.889) | 0.613 |
| rs3748816 | | | 0.513 | | | | 0.581 | | | | 0.390 | | |
| AA/AG | 93 (83.0) | 12 (6.1-17.9) | | 1 | | 28 (14.7-41.3) | | 1 | | 25 (16.5-33.5) | | 1 | |
| GG | 18 (16.1) | 11 (4.8-17.2) | | 0.823 (0.453-1.496) | 0.523 | 27 (20.1-33.9) | | 0.841 (0.451-1.568) | 0.585 | 27 (20.1-33.9) | | 0.773 (0.426-1.402) | 0.397 |
| rs7528484 | | | 0.188 | | | | 0.078 | | | | 0.193 | | |
| CC/CT | 86 (76.8) | 10 (5.5-14.5) | | 1 | | 29 (19.7-38.3) | | 1 | | 25 (19.3-30.7) | | 1 | |
| TT | 26 (23.2) | 15 (10.4-19.6) | | 0.691 (0.392-1.217) | 0.201 | 21 (0-48.2) | | 0.601 (0.321-1.126) | 0.112 | 32 (0-77.8) | | 0.699 (0.404-1.209) | 0.200 |
| Co-dominant model | | | | | | | | | | | | | |
| rs10740055 | | | 0.034 | | | | 0.093 | | | | 0.060 | | |
| CC | 27 (24.1) | 10 (5.1-14.9) | | 1 | | 30 (6.5-53.5) | | 1 | | 29 (11.9-46.1) | | 1 | |
| CA | 58 (51.8) | 16 (12.3-19.7) | | 1.275 (0.711-2.288) | 0.415 | 31 (18.8-43.2) | | 1.007 (0.557-1.821) | 0.981 | 28 (19.8-36.2) | | 0.987 (0.572-1.702) | 0.962 |
| AA | 26 (23.2) | 8 (3.9-12.1) | | 2.208 (1.138-4.286) | 0.019 | 16 (8.3-23.7) | | 1.785 (0.917-3.475) | 0.088 | 12 (3.0-21.0) | | 1.775 (0.957-3.289) | 0.068 |
| rs11168249 | | | 0.180 | | | | 0.231 | | | | 0.360 | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TT | 33 (29.5) | 8 (2.7-13.3) | | 1 | | 20 (17.3-22.7) | | 1 | | 20 (16.7-23.3) | | 1 | |
| TC | 61 (54.5) | 17 (11.3-22.7) | | 0.765 (0.462-1.268) | 0.299 | 38 (22.6-53.4) | | 0.647 (0.385-1.087) | 0.100 | 29 (16.3-41.7) | | 0.767 (0.469-1.254) | 0.290 |
| CC | 18 (16.1) | 7 (4.6-9.4) | | 1.353 (0.678-2.701) | 0.391 | 31 (17.5-44.5) | | 0.880 (0.431-1.796) | 0.726 | 24 (9.4-38.6) | | 1.121 (0.582-2.158) | 0.733 |
| rs1137101 | | | 0.014 | | | | 0.262 | | | | 0.452 | | |
| AA | 29 (25.9) | 18 (0-48.5) | | 1 | | 41 (21.5-60.5) | | 1 | | 31 (7.6-54.4) | | 1 | |
| AG | 54 (48.2) | 13 (3.4-19.7) | | 1.445 (0.781-2.675) | 0.241 | 30 (12.6-47.4) | | 1.102 (0.598-2.031) | 0.755 | 28 (12.1-43.9) | | 0.919 (0.537-1.574) | 0.760 |
| GG | 29 (25.9) | 7 (6.2-7.8) | | 2.464 (1.268-4.790) | 0.008 | 20 (12.2-27.8) | | 1.609 (0.832-3.111) | 0.157 | 20 (13.0-27.0) | | 1.271 (0.706-2.290) | 0.424 |
| rs2736100 | | | 0.980 | | | | 0.671 | | | | 0.422 | | |
| CC | 31 (27.7) | 11 (4.8-17.2) | | 1 | | 22 (12.9-31.1) | | 1 | | 20 (11.8-28.2) | | 1 | |
| CA | 44 (39.3) | 15 (8.9-21.1) | | 0.966 (0.559-1.670) | 0.902 | 32 (20.3-43.7) | | 0.784 (0.442-1.391) | 0.405 | 32 (20.3-43.7) | | 0.713 (0.414-1.230) | 0.224 |
| AA | 29 (25.9) | 11 (5.7-16.4) | | 1.022 (0.548-1.906) | 0.946 | 29 (10.0-48.0) | | 0.792 (0.404-1.552) | 0.497 | 20 (7.5-30.5) | | 0.924 (0.509-1.678) | 0.795 |
| rs3748816 | | | 0.282 | | | | 0.639 | | | | 0.688 | | |
| AA | 43 (38.4) | 16 (8.4-23.6) | | 1 | | 41 (17.9-64.1) | | 1 | | 22 (1.0-43.0) | | 1 | |
| AG | 50 (44.6) | 8 (2.6-13.4) | | 1.432 (0.862-2.380) | 0.166 | 25 (16.0-34.0) | | 1.224 (0.721-2.081) | 0.454 | 25 (15.9-34.1) | | 0.978 (0.606-1.578) | 0.926 |
| GG | 18 (16.1) | 11 (4.8-17.2) | | 1.005 (0.514-1.965) | 0.989 | 27 (20.1-33.9) | | 0.944 (0.469-1.900) | 0.872 | 27 (20.1-33.9) | | 0.764 (0.399-1.462) | 0.416 |
| rs7528484 | | | 0.238 | | | | 0.177 | | | | 0.212 | | |
| CC | 32 (28.6) | 18 (5.6-30.4) | | 1 | | 30 (22.1-37.9) | | 1 | | 28 (19.9-36.0) | | 1 | |
| CT | 54 (48.2) | 10 (5.1-14.9) | | 1.304 (0.775-2.194) | 0.318 | 25 (19.2-30.9) | | 1.265 (0.740-2.163) | 0.390 | 22 (13.9-30.1) | | 1.343 (0.806-2.239) | 0.258 |
| TT | 26 (23.2) | 15 (10.4-19.6) | | 0.807 (0.420-1.549) | 0.519 | 86 (55.0-117.4) | | 0.693 (0.339-1.414) | 0.313 | 32 (0-77.8) | | 0.831 (0.440-1.570) | 0.569 |
| Dominant model | | | | | | | | | | | | | |
| rs10740055 | | | 0.152 | | | | 0.536 | | | | 0.549 | | |
| CC | 27 (24.1) | 10 (5.1-14.9) | | 1 | | 30 (6.5-53.5) | | 1 | | 29 (11.9-46.1) | | 1 | |
| AA/CA | 84 (75.0) | 13 (7.1-18.9) | | 1.485 (0.851-2.590) | 0.164 | 27 (17.5-36.5) | | 1.190 (0.681-2.081) | 0.541 | 24 (17.5-30.5) | | 1.168 (0.699-1.952) | 0.554 |
| rs11168249 | | | 0.512 | | | | 0.136 | | | | 0.439 | | |
| TT | 33 (29.5) | 8 (2.7-13.3) | | 1 | | 20 (17.3-22.7) | | 1 | | 20 (16.7-23.3) | | 1 | |
| CC/TC | 79 (70.6) | 13 (6.3-19.7) | | 0.855 (0.528-1.382) | 0.522 | 31 (19.3-42.8) | | 0.692 (0.424-1.131) | 0.142 | 28 (18.9-37.1) | | 0.833 (0.523-1.329) | 0.444 |
| rs1137101 | | | 0.059 | | | | 0.424 | | | | 0.902 | | |
| AA | 29 (25.9) | 18 (0-48.5) | | 1 | | 41 (21.5-60.5) | | 1 | | 31 (7.6-54.4) | | 1 | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GG/AG | 83 (74.1) | 10 (6.5-13.5) | | 1.719 (0.960-3.079) | 0.068 | 25 (18.0-32.0) | | 1.286 (0.917-1.803) | 0.145 | 25 (17.9-32.1) | | 1.031 (0.627-1.698) | 0.903 |
| rs2736100 | | | 0.955 | | | | 0.372 | | | | 0.335 | | |
| CC | 31 (27.7) | 11 (4.8-17.2) | | 1 | | 22 (12.9-31.1) | | 1 | | 20 (11.8-28.2) | | 1 | |
| AA/CA | 73 (65.2) | 12 (7.0-17.0) | | 0.986 (0.596-1.631) | 0.956 | 32 (22.7-41.3) | | 0.787 (0.462-1.340) | 0.377 | 29 (19.1-38.9) | | 0.786 (0.478-1.291) | 0.341 |
| rs3748816 | | | 0.287 | | | | 0.613 | | | | 0.682 | | |
| AA | 43 (38.4) | 16 (8.4-23.6) | | 1 | | 41 (17.9-64.1) | | 1 | | 22 (1.0-43.0) | | 1 | |
| GG/AG | 68 (60.7) | 10 (5.8-14.2) | | 1.290 (0.798-2.086) | 0.299 | 27 (22.0-32.0) | | 1.137 (0.688-1.877) | 0.617 | 27 (22.4-37.6) | | 0.911 (0.581-1.428) | 0.685 |
| rs7528484 | | | 0.673 | | | | 0.837 | | | | 0.581 | | |
| CC | 32 (28.6) | 18 (5.6-30.4) | | 1 | | 30 (22.1-37.9) | | 1 | | 28 (20.0-36.0) | | 1 | |
| TT/CT | 80 (71.4) | 11 (7.1-14.9) | | 1.109 (0.679-1.812) | 0.680 | 27 (13.0-41.0) | | 1.055 (0.632-1.759) | 0.838 | 24 (16.9-31.1) | | 1.144 (0.706-1.853) | 0.585 |

[1]Kaplan-Meier survival analysis.

[2]Univariate Cox regression analyses.

SNP: Single-nucleotide polymorphism; CI: Confidence interval; HR: Hazard ratio.

In multivariable Cox regression analysis, no SNP retained independent prognostic significance. Independent adverse clinical predictors included low hemoglobin (RFS, CSS, OS), intraoperative FFP transfusion (all outcomes), MVI (all outcomes), tumor grade G3-G4 (all outcomes), advanced pT/pN stage (CSS, OS), and severe postoperative complications (Clavien-Dindo ≥ III, OS only) (Table 5). In the pCCA cohort, the PH assumption was largely fulfilled across all multivariable models (Supplementary Table 7). A moderate correlation between partial residuals and ranked survival time was observed for intraoperative FFP transfusion in the RFS model ($r$ = 0.326, $P$ = 0.012). Additionally, trend-level correlations were noted for N1 and T stage in the OS model. However, these correlations were limited in magnitude and did not indicate systematic time-dependent effects. No violations of the PH assumption were detected for the primary genetic variable rs10740055. In the pCCA cohort, EPV values were within or close to commonly accepted thresholds (EPV 9.8-12.2; Supplementary Table 8), and reduced-model sensitivity analyses showed largely consistent HR estimates for the main clinical predictors (tumor grading and N category) across endpoints, with only minor attenuation for selected associations (Supplementary Table 9).

## DISCUSSION

In this genetic association study of CCA, we identified two SNPs with significant prognostic relevance. Carriers of the variant allele of rs10740055 in *ARID5B* showed markedly poorer RFS, CSS, and OS in both iCCA and pCCA cohorts in univariate analyses. Notably, the prognostic impact of *ARID5B* remained significant in multivariate Cox models for iCCA, indicating that rs10740055 is an independent predictor of outcome in this subgroup. The *LEPR* rs1137101 polymorphism was also associated with shorter RFS in iCCA, particularly in patients with the GG genotype, although this effect was not observed in pCCA. In contrast, none of the other six candidate SNPs reached statistical significance for

**Table 3 Multivariable Cox regression analysis of recurrence-free survival, cancer-specific survival and overall survival in intrahepatic cholangiocarcinoma**

| Variables | Recurrence-free survival | | Cancer-specific survival | | Overall survival | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | *P* value | HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Neoadjuvant therapy (no = 1) | 5.346 (1.737-16.455) | 0.003 | | | | |
| LVI (no = 1) | 3.749 (1.895-7.418) | < 0.001 | | | 5.524 (2.600-11.738) | < 0.001 |
| Hemoglobin, g/L (≤ 12 = 1) | | | 0.438 (0.222-0.867) | 0.018 | 0.078 (0.013-0.486) | 0.006 |
| N category (pN0 = 1) | | | 3.562 (1.802-7.041) | < 0.001 | | |
| rs10740055 (CC/CA = 1) | 2.413 (1.311-4.440) | 0.005 | 2.265 (1.137-4.513) | 0.020 | 4.095 (1.966-8.529) | < 0.001 |

Only significant parameters are shown. LVI: Lymph vascular invasion; CI: Confidence interval; HR: Hazard ratio.

survival, highlighting the specificity of *ARID5B* and *LEPR* variants as key germline genetic factors linked to post-resection outcomes in this cohort.

These findings underscore *ARID5B* and *LEPR* as potential contributors to CCA progression, aligning with and extending prior knowledge from other malignancies. To better contextualize this finding, the biological functions of *ARID5B* and its potential role in tumor development warrant further consideration. *ARID5B* encodes a transcriptional co-regulator involved in diverse biological processes it binds A/T-rich DNA sequences and interacts with epigenetic modifiers (like *PHD* finger protein 2) to activate gene transcription in metabolic and developmental pathways. Germline polymorphisms in *ARID5B* (including rs10740055, located in intron 3) have been previously linked to cancer susceptibility and outcomes in hematologic malignancies, most notably pediatric acute lymphoblastic leukemia[10,11]. Importantly, recent evidence suggests a role for *ARID5B* in solid tumors as well. In hepatocellular carcinoma, *ARID5B* has been shown to interact with histone deacetylase 1, influencing cell proliferation and differentiation, with high *ARID5B* expression correlating with shorter OS[12]. Similarly, *ARID5B* downregulation has been observed in breast cancers, where it appears to suppress cell proliferation[13]. However, data on *ARID5B* SNPs, including rs10740055, in solid malignancies remain limited, underscoring the novelty and potential significance of our findings in CCA.

To the best of our knowledge, this is the first study to report a prognostic role of an *ARID5B* SNP not only in hepatobiliary malignancies but all solid cancers. One plausible mechanism is that *ARID5B* influences the tumor microenvironment through immuno-regulatory effects. The *ARID5B* gene has been implicated in the regulation of mitochondrial membrane potential, the transcription of genes encoding components of the electron transport chain, and oxidative metabolism[14]. It also plays a pivotal role in the development of B-cell progenitors[15]. *ARID5B* has further been reported to modulate androgen receptor gene transcription *via* histone methylation[16]. Moreover, the *ARID* protein family is believed to participate in transcriptional regulation, cellular differentiation, proliferation, and development, and is closely associated with cancer-related signaling pathways[17]. The rs10740055 variant is predicted to alter exonic splicing enhancer binding motifs, potentially disrupting the interaction with the splicing regulator SF2/ASF (immunoglobulin M-*BRCA1*), thereby suggesting a role in epigenetic modulation. Notably, the binding site is shifted four nucleotides upstream, which could interfere with covalent or non-covalent protein interactions and compromise functional efficacy[18]. Furthermore, linkage disequilibrium mapping identified several neighboring variants in close proximity to rs10740055, suggesting potential synergistic contributions to disease susceptibility[19]. Recent work has shown that *ARID5B* can act as a negative regulator of pro-inflammatory cytokine production for example, knockdown of *ARID5B* leads to increased interleukin-6 (IL-6) expression in activated stromal cells. IL-6/signal transducer and activator of transcription 3 (STAT3) signaling is a known driver of CCA growth and survival, conferring resistance to apoptosis and therapy[20]. Thus, an inherited *ARID5B* variant that diminishes *ARID5B* function or expression could tilt the inflammatory milieu toward higher IL-6 levels, in turn promoting more aggressive tumor behavior. Although direct evidence in CCA is lacking, the convergence of our clinical data with *ARID5B*'s known functions (in inflammatory regulation and lymphocyte development) supports a model whereby this gene modulates tumor progression, potentially by shaping both intrinsic tumor cell properties and the host immune response.

The prognostic association of the leptin receptor gene *LEPR* (rs1137101) with RFS in iCCA also merits discussion in light of existing literature. Leptin, a hormone predominantly produced by adipose tissue, has well-established pro-tumorigenic effects in gastrointestinal cancers. In CCA models, leptin and its receptor drive malignant behavior: Leptin stimulation activates Janus kinases/STAT3 and extracellular regulated protein kinases pathways in cholangiocytes, thereby enhancing cell proliferation, migration, and resistance to apoptosis[21]. Moreover, experimental disruption of leptin-*LEPR* signaling (for instance, using leptin receptor-deficient fa/fa rats) significantly reduces CCA development and growth[21]. Our finding that rs113710 is linked to early tumor recurrence in iCCA patients is biologically plausible given this context. The rs1137101 results in an amino acid change in the *LEPR* and is a common functional polymorphism; notably, the rs1137101 G-allele has been associated with altered receptor signaling and a predisposition to metabolic syndrome (including higher rates of obesity and type 2 diabetes). It is conceivable that patients with the GG genotype experience a more pro-oncogenic metabolic-inflammatory state for example, *via* elevated leptin levels or sensitivity which could accelerate cancer recurrence. Leptin acts not only as a mitogen for cholangiocytes but also as an immunomodulatory cytokine, promoting a T helper cell 1 inflammatory response and macrophage activation in the tumor microenvir-

**Table 4 Single nucleotide polymorphism frequencies and associations with recurrence-free survival, cancer-specific survival and overall survival in perihilar cholangiocarcinoma**

| SNP | *n* (%) | Recurrence-free survival | | | | Cancer-specific survival | | | | Overall survival | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Median (95%CI) | *P* value[1] | HR (95%CI) | *P* value[2] | Median (95%CI) | *P* value[1] | HR (95%CI) | *P* value[2] | Median (95%CI) | *P* value[1] | HR (95%CI) | *P* value[2] |
| Recessive model | | | | | | | | | | | | | |
| rs10740055 | | | 0.027 | | | | 0.004 | | | | < 0.001 | | |
| CC/CA | 85 (72.6) | 52 (22.1-81.9) | | 1 | | 65 (31.8-98.2) | | 1 | | 50 (38.7-61.3) | | 1 | |
| AA | 32 (27.4) | 15 (9.4-20.6) | | 1.840 (1.057-3.200) | 0.031 | 19 (8.7-29.3) | | 2.184 (1.262-3.781) | 0.005 | 14 (8.5-19.5) | | 1.840 (1.057-3.200) | 0.001 |
| rs1137101 | | | 0.460 | | | | 0.843 | | | | 0.647 | | |
| AA/AG | 92 (78.7) | 31 (15.8-46.2) | | 1 | | 45 (28.5-61.5) | | 1 | | 32 (22.2-41.8) | | 1 | |
| GG | 25 (21.4) | 52 (25.0-79.0) | | 0.790 (0.420-1.486) | 0.464 | 63 (19.4-106.6) | | 0.941 (0.516-1.718) | 0.844 | 54 (13.8-94.2) | | 0.890 (0.537-1.473) | 0.650 |
| rs3184504 | | | 0.072 | | | | 0.070 | | | | 0.423 | | |
| TT/TC | 92 (78.6) | 52 (18.6-85.4) | | 1 | | 63 (36.0-90.0) | | 1 | | 39 (22.5-55.5) | | 1 | |
| CC | 32 (27.4) | 19 (10.1-27.9) | | 1.618 (0.949-2.758) | 0.077 | 29 (16.8-41.2) | | 1.102 (0.625-1.941) | 0.737 | 19 (7.0-31.0) | | 1.214 (0.752-1.960) | 0.428 |
| rs3130 | | | 0.841 | | | | 0.934 | | | | 0.448 | | |
| TT/TC | 79 (67.6) | 31 (13.0-49.0) | | 1 | | 50 (28.2-71.8) | | 1 | | 32 (21.1-42.9) | | 1 | |
| CC | 26 (22.2) | 52 (0-106.2) | | 1 (0.999-1.001) | 0.586 | 33 (0-87.3) | | 1.000 (0.999-1.001) | 0.804 | 30 (0-69.7) | | 1.000 (0.999-1.000) | 0.257 |
| rs3748816 | | | 0.616 | | | | 0.211 | | | | 0.668 | | |
| AA/AG | 105 (89.7) | 39 (23.6-54.4) | | 1 | | 51 (28.3-73.7) | | 1 | | 38 (22.8-53.2) | | 1 | |
| GG | 12 (10.3) | 24 (12.8-35.3) | | 1.207 (0.574-2.535) | 0.620 | 28 (20.4-35.6) | | 1.562 (0.769-3.174) | 0.217 | 26 (20.9-31.1) | | 1.154 (0.596-2.232) | 0.672 |
| rs7528484 | | | 0.626 | | | | 0.793 | | | | 0.343 | | |
| CC/CT | 100 (85.5) | 36 (24.0-48.0) | | 1 | | 50 (23.9-76.1) | | 1 | | 38 (25.0-51.0) | | 1 | |
| TT | 17 (14.5) | 55 (8.4-101.6) | | 0.824 (0.375-1.810) | 0.629 | 84 (0-235.9) | | 0.949 (0.451-1.998) | 0.891 | 27 (4.1-49.6) | | 1.306 (0.747-2.281) | 0.349 |
| Co-dominant model | | | | | | | | | | | | | |
| rs10740055 | | | 0.060 | | | | 0.015 | | | | 0.002 | | |
| CC | 32 (27.4) | 42 (29.5-54.5) | | 1 | | 76 (39.9-112.1) | | 1 | | 63 (45.3-80.8) | | 1 | |
| CA | 53 (45.3) | 67 (18.7-115.3) | | 0.759 (0.423-1.363) | 0.356 | 63 (23.3-102.7) | | 0.913 (0.494-1.685) | 0.770 | 41 (22.1-60.0) | | 1.218 (0.719-2.064) | 0.462 |
| AA | 32 (27.4) | 15 (9.4-20.6) | | 1.582 (0.842-2.971) | 0.154 | 19 (8.7-29.3) | | 2.070 (1.077-3.977) | 0.029 | 14 (8.5-19.5) | | 2.467 (1.392-4.373) | 0.002 |
| rs1137101 | | | 0.626 | | | | 0.962 | | | | 0.842 | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AA | 34 (29.1) | 24 (0-49.8) | | 1 | | 51 (0-106.3) | | 1 | | 29 (7.4-50.6) | | 1 | |
| AG | 58 (49.6) | 42 (2.9-81.1) | | 0.842 (0.482-1.472) | 0.547 | 45 (28.5-61.5) | | 1.061 (0.584-1.927) | 0.847 | 32 (23.1-40.9) | | 1.096 (0.664-1.808) | 0.721 |
| GG | 25 (21.4) | 52 (25.0-79.0) | | 0.712 (0.350-1.450) | 0.349 | 63 (19.4-106.6) | | 0.976 (0.480-1.985) | 0.947 | 54 (13.8-94.2) | | 0.942 (0.519-1.709) | 0.843 |
| rs3184504 | | | 0.130 | | | | 0.180 | | | | 0.723 | | |
| TT | 28 (23.9) | 83 (58.2-107.5) | | 1 | | 80.2 (56.6-103.8) | | 1 | | 38 (22.3-53.7) | | 1 | |
| TC | 57 (48.7) | 45 (18.5-71.5) | | 1.404 (0.707-2.787) | 0.332 | 63 (30.2-95.8) | | 1.154 (0.588-2.264) | 0.677 | 49 (27.3-70.7) | | 0.977 (0.579-1.649) | 0.931 |
| CC | 32 (27.4) | 19 (10.1-27.9) | | 2.058 (0.984-4.302) | 0.055 | 29 (16.8-41.2) | | 1.798 (0.878-3.683) | 0.109 | 19 (7.0-31.0) | | 1.195 (0.661-2.163) | 0.556 |
| rs3130 | | | 0.652 | | | | 0.926 | | | | 0.863 | | |
| TT | 34 (29.1) | 78 (25.7-130.3) | | 1 | | 45 (0-106.1) | | 1 | | 28 (10.9-45.1) | | 1 | |
| TC | 45 (38.5) | 25 (5.3-44.7) | | 0.875 (0.590-1.299) | 0.508 | 50 (34.4-65.6) | | 0.908 (0.458-1.801) | 0.782 | 38 (15.9-60.1) | | 0.987 (0.591-1.647) | 0.960 |
| CC | 26 (22.2) | 52 (0-106.2) | | 1.164 (0.818-1.657) | 0.398 | 33 (0-87.3) | | 1.200 (0.629-2.290) | 0.580 | 30 (0-69.7) | | 0.859 (0.473-1.562) | 0.619 |
| rs3748816 | | | 0.373 | | | | 0.217 | | | | 0.589 | | |
| AA | 50 (42.7) | 37 (19.9-54.1) | | 1 | | 50 (22.8-77.2) | | 1 | | 33 (20.2-45.7) | | 1 | |
| AG | 55 (47.0) | 42 (0-96.1) | | 0.702 (0.413-1.192) | 0.190 | 78 (61.9-94.2) | | 0.708 (0.410-1.222) | 0.215 | 49 (29.2-68.8) | | 0.808 (0.517-1.264) | 0.351 |
| GG | 12 (10.3) | 24 (12.8-35.3) | | 1.005 (0.459-2.199) | 0.990 | 28 (20.4-35.6) | | 1.312 (0.619-2.785) | 0.479 | 26 (21.0-31.1) | | 1.033 (0.515-2.071) | 0.927 |
| rs7528484 | | | 0.855 | | | | 0.758 | | | | 0.471 | | |
| CC | 36 (30.8) | 40 (13.1-66.9) | | 1 | | 50 (9.3-90.7) | | 1 | | 41 (22.4-59.6) | | 1 | |
| CT | 64 (54.7) | 31 (14.4-47.6) | | 1.077 (0.626-1.854) | 0.788 | 45 (24.8-65.2) | | 1.231 (0.701-2.162) | 0.469 | 31 (16.2-45.8) | | 1.214 (0.749-1.968) | 0.431 |
| TT | 17 (14.5) | 55 (8.4-101.6) | | 0.862 (0.366-2.031) | 0.735 | 65 (10.4-119.6) | | 1.079 (0.472-2.465) | 0.858 | 27 (4.1-49.9) | | 1.470 (0.778-2.777) | 0.236 |
| Dominant model | | | | | | | | | | | | | |
| rs10740055 | | | 0.936 | | | | 0.506 | | | | 0.081 | | |
| CC | 32 (27.4) | 42 (29.5-54.5) | | 1 | | 76 (39.9-112.1) | | 1 | | 63 (45.2-80.8) | | 1 | |
| AA/CA | 85 (72.7) | 29 (13.4-44.6) | | 0.979 (0.583-1.646) | 0.937 | 39 (23.5-54.4) | | 1.205 (0.693-2.095) | 0.509 | 30 (23.0-37.0) | | 1.531 (0.941-2.491) | 0.087 |
| rs1137101 | | | 0.400 | | | | 0.912 | | | | 0.865 | | |
| AA | 34 (29.0) | 24 (0-49.8) | | 1 | | 28 (0-106.3) | | 1 | | 29 (7.4-50.6) | | 1 | |
| GG/AG | 83 (71.0) | 42 (17.0-67.0) | | 0.800 (0.474-1.352) | 0.405 | 14 (21.2-76.8) | | 0.992 (0.700-1.404) | 0.963 | 33 (19.5-46.5) | | 1.041 (0.650-1.667) | 0.866 |
| rs3184504 | | | 0.150 | | | | 0.344 | | | | 0.863 | | |
| TT | 28 (23.9) | 82.8 (58.2-107.5) | | 1 | | 80.2 (56.6-103.8) | | 1 | | 38 (22.3-53.7) | | 1 | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CC/TC | 89 (76.1) | | | 1.599 (0.834-3.065) | 0.158 | 49 (22.0-76.0) | | 1.353 (0.719-2.545) | 0.349 | 32 (16.5-47.5) | | 1.044 (0.638-1.707) | 0.864 |
| rs3130 | | | 0.636 | | | | 0.878 | | | | 0.504 | | |
| TT | 34 (29.1) | 78 (25.7-130.3) | | 1 | | 45 (0-106.1) | | 1 | | 28 (10.9-45.1) | | 1 | |
| CC/TC | 71 (60.7) | 29 (11.8-46.2) | | 1 (0.999-1.001) | 0.587 | 50 (29.5-70.5) | | 1.000 (0.999-1.001) | 0.804 | 38 (16.9-59.1) | | 1.000 (0.999-1.000) | 0.258 |
| rs3748816 | | | 0.262 | | | | 0.408 | | | | 0.436 | | |
| AA | 50 (42.7) | 37 (19.9-54.1) | | 1 | | 50 (22.8-77.2) | | 1 | | 33 (20.3-45.7) | | 1 | |
| GG/AG | 67 (57.3) | 39 (0-83.3) | | 0.755 (0.460-1.240) | 0.268 | 49 (12.4-85.6) | | 1.000 (0.999-1.001) | 0.804 | 38 (20.3-55.7) | | 0.847 (0.555-1.293) | 0.441 |
| rs7528484 | | | 0.900 | | | | 0.510 | | | | 0.305 | | |
| CC | 36 (30.8) | 40 (13.1-66.9) | | 1 | | 50 (9.3-90.7) | | 1 | | 41 (22.4-59.6) | | 1 | |
| TT/CT | 81 (69.2) | 36 (18.4-53.6) | | 1.034 (0.611-1.749) | 0.901 | 49 (16.2-81.8) | | 1.199 (0.696-2.063) | 0.513 | 31 (18.8-43.2) | | 1.269 (0.801-2.011) | 0.310 |

[1]Kaplan-Meier survival analysis.

[2]Univariate Cox regression analyses.

SNP: Single-nucleotide polymorphism; CI: Confidence interval; HR: Hazard ratio.

onment. Thus, the *LEPR* rs1137101 variant might influence CCA outcomes by modifying the intensity of leptin signaling cascades that support tumor growth. Although prior studies examining *LEPR* rs1137101 in cancer have mostly focused on risk rather than prognosis (with mixed results in breast and other cancers) our data suggest this host genetic factor has prognostic relevance in iCCA[22].

It is also notable that no other SNPs showed significant associations, underscoring the specificity of the *ARID5B* and *LEPR* findings. Several of the SNPs we tested were hypothesized to affect immune pathways or oncogenic signaling in CCA; the lack of significance for those markers may reflect true null effects or simply insufficient power to detect modest impacts. Previous candidate-gene studies in CCA have reported prognostic SNPs in a variety of pathways, for example, polymorphisms inflammation-related genes were found to correlate with survival in iCCA[8]. The consistent adverse effect of the *ARID5B* risk allele across both iCCA and pCCA, and of the *LEPR* variant in iCCA, suggests that germline genetic makeup including pathways related to adipogenesis, metabolism, and cytokine signaling can influence the clinical course of biliary tract cancers. These findings contribute to a growing body of evidence that inherited variations, though subtle, may modify tumor behavior and patient outcomes in CCA.

PCCA and iCCA arise in very different clinical and etiologic settings[23,24]. ICCA often occur in the context of chronic liver disease (viral hepatitis, fluke infection or cirrhosis), whereas pCCA are most strongly linked to primary sclerosing cholangitis and large-duct biliary inflammation[23]. These divergent pathways imply distinct tumor microenvironments and cells of origin: For example, iCCA tumors frequently derive from small intrahepatic bile ducts or hepatic progenitor cells, while pCCA stems from mucin-secreting cholangiocytes of large ducts[23]. Transcriptomic profiling studies echo these differences. Some analyses find that pCCAs are molecularly similar to the “large-duct” subtype of iCCA, but others reveal unique patterns[25]. Overall, pCCA (and distal CCA) frequently harbor *KRAS*, *TP53* and *ARID1A* mutations, whereas iCCA cases include distinct subsets (*e.g.*, *FGFR2*-fusion or *IDH1*-mutant tumors)[24]. These genomic landscapes imply different dominant oncogenic pathways that drive prognosis. It is plausible that rs10740055 exerts its influence

**Table 5 Multivariable Cox regression analysis of recurrence-free survival, cancer-specific survival and overall survival in perihilar cholangiocarcinoma**

| Variables | Recurrence-free survival | | Cancer-specific survival | | Overall survival | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | *P* value | HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Hemoglobin, g/L (≤ 12 = 1) | 0.274 (0.146-0.516) | < 0.001 | 0.347 (0.180-0.668) | 0.002 | 0.385 (0.226-0.654) | < 0.001 |
| Intraoperative FFP (no = 1) | 2.868 (1.501-5.480) | 0.001 | 4.340 (2.094-8.994) | < 0.001 | 3.072 (1.762-3.354) | < 0.001 |
| MVI (no = 1) | 48.237 (8.791-264.662) | < 0.001 | 50.516 (8.685-293.835) | < 0.001 | 19.083 (3.880-93.844) | < 0.001 |
| Tumor grading (G1/G2 = 1) | 3.740 (1.711-8.177) | < 0.001 | 4.637 (2.109-10.193) | < 0.001 | 3.699 (1.879-7.284) | < 0.001 |
| pT category (pT1-2 = 1) | | | 2.573 (1.358-4.877) | 0.004 | 2.227 (1.309-3.789) | 0.003 |
| N category (pN0 = 1) | 2.704 (1.476-4.954) | 0.001 | 2.524 (1.374-4.634) | 0.003 | 1.779 (1.055-2.998) | 0.031 |
| Perioperative complications (Clavien-Dindo) (0/I/II = 1) | | | | | 2.115 (1.279-3.497) | 0.004 |

Only significant parameters are shown. FFP: Fresh frozen plasma; MVI: Microvascular invasion; CI: Confidence interval; HR: Hazard ratio.

only in a particular biological context (for instance, in the inflammatory milieu of iCCA) and is muted when other potent drivers predominate, as in pCCA[24].

Our results have potential clinical implications for postoperative risk stratification in CCA. Prognosis after curative-intent resection of CCA currently hinges on pathological features such as tumor stage, margin status, and lymph node involvement. The addition of germline genetic markers like *ARID5B* rs10740055 and *LEPR* rs1137101 could refine this risk assessment by identifying patients who are biologically predisposed to early recurrence or cancer-related mortality, independent of classical clinicopathologic factors. For instance, an iCCA patient harboring the high-risk *ARID5B* allele might have an elevated risk of relapse even if their tumor is early stage; recognizing this upfront could encourage more aggressive adjuvant therapy or closer surveillance. As SNPs can be easily assessed by simple blood samples, incorporating SNP-based stratification into clinical practice could personalize post-surgical management: High-risk genotypes might prompt intensified monitoring protocols or enrollment in adjuvant trials, whereas patients without risk alleles might be candidates for standard follow-up.

This is particularly relevant for pCCA, where curative-intent resection remains the only potentially curative treatment option. However, surgery is technically complex and associated with high morbidity and mortality compared to other solid malignancies[26,27]. Recent data from a large single-center cohort demonstrated that approximately one-third of patients undergoing surgical exploration for pCCA were ultimately deemed unresectable due to factors such as vascular infiltration, peritoneal carcinomatosis, or insufficient liver function[27]. Thus, the identification of oncological risks prior to surgery is helpful for a tailored approach to identify patients which have notable oncological benefits from high-risk surgical procedures.

Notably, germline SNPs are attractive as biomarkers because they are stable and easily assayed, and they precede the development of cancer allowing risk prediction at the time of surgery or even beforehand[28]. Our findings reinforce the concept that genomic medicine can extend beyond tumor sequencing into the realm of host genetics. In the long term, a panel of prognostic SNPs might join other emerging biomarkers (such as circulating tumor DNA and inflammatory indices) to improve outcome prediction in CCA[7]. Such an approach aligns with the trend toward precision oncology, where treatment intensity and surveillance can be tailored to an individual's risk profile. Ultimately, validating SNP-based risk models in CCA could help guide adjuvant therapy decisions (for example, identifying which patients are most likely to benefit from chemotherapy or experimental immunotherapy) and inform follow-up scheduling, with the goal of improving survival through proactive, personalized care.

This study has several limitations that should be acknowledged. The overall sample size was relatively modest, particularly after stratification into intrahepatic and pCCA sub-cohorts. However, our study represents one of the largest well-characterized cohorts evaluating germline SNPs in surgically treated CCA currently available in the literature. While rs10740055 (*ARID5B*) demonstrated a consistent effect across both tumor subtypes, the smaller size of the pCCA subgroup may have reduced the statistical power to detect its independent prognostic value in multivariable analyses. Consequently, the study may be underpowered to identify more subtle associations for other SNPs or within specific subgroups. Nevertheless, given the rarity of CCA, the cohort size appears appropriate to address the primary research question. Moreover, the stability of the multivariable models was supported by acceptable EPV ratios across the analyzed endpoints (Supplementary Table 8). By focusing on a clinically meaningful subgroup of patients undergoing curative-intent surgery and excluding perioperative mortality, we established a relatively small but well-characterized cohort that allowed multivariable analyses incorporating key prognostic factors such as pathological staging. Future multicenter studies with larger patient populations will be required to further validate these findings and assess the prognostic value of germline polymorphisms across different CCA subtypes.

Furthermore, several polymorphisms were analyzed across multiple survival endpoints, including RFS, CSS and OS. As a result, the possibility of type I error due to multiple testing cannot be completely excluded. Because the present

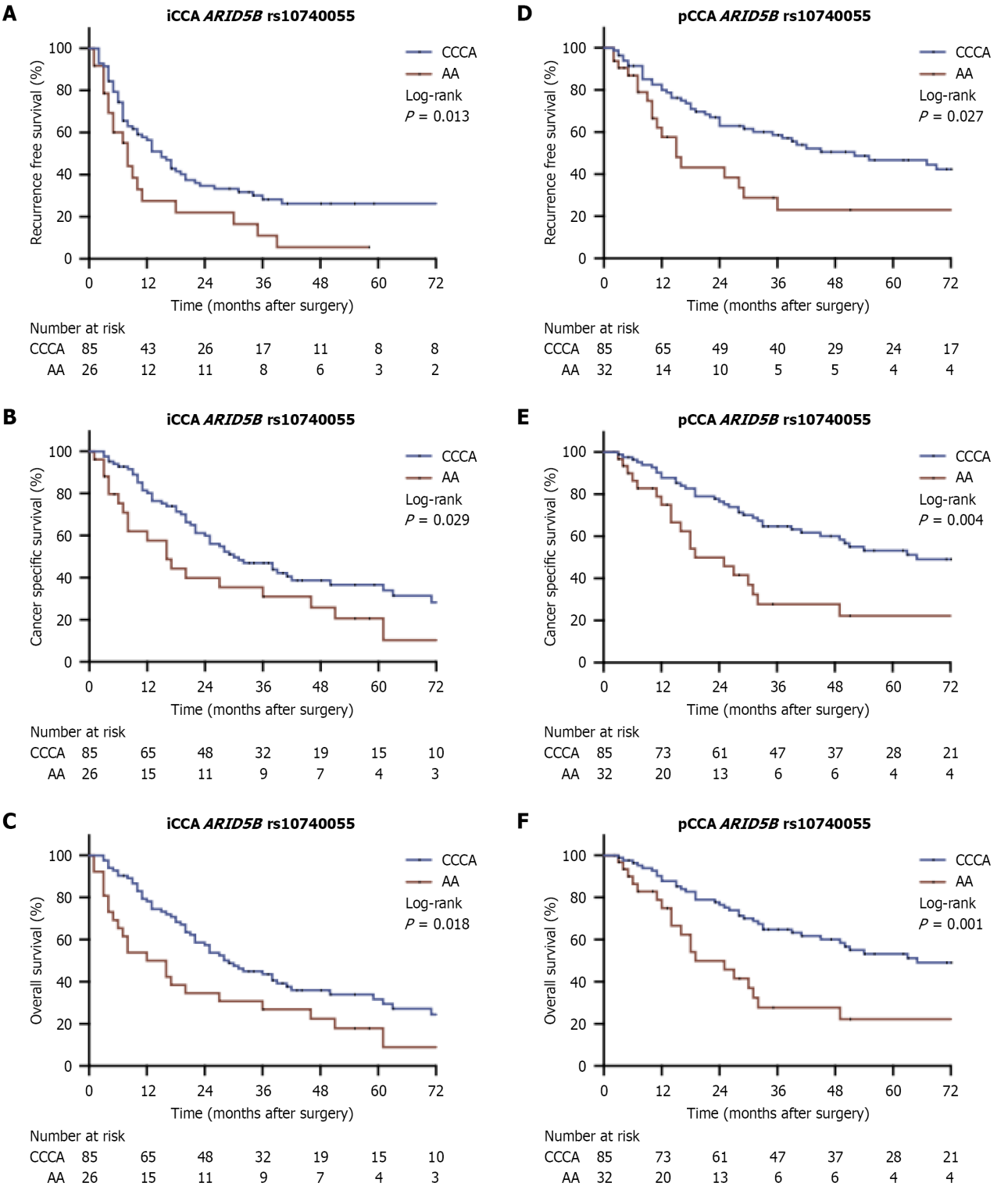



**Figure 1 Survival in cholangiocarcinoma with respect to *ARID5B* rs10730055.** Survival figures after curative-intent surgery for intrahepatic cholangiocarcinoma (iCCA) and perihilar cholangiocarcinoma (pCCA) are displayed. A-C: The median recurrence-free survival (RFS) (A), overall survival (OS) (B) and cancer-specific survival (CSS) (C) after resection for iCCA were 13 months, 30 months and 28 months for the CC/CA genotype and 8 months, 16 months, 12 months for the AA genotype; D-F: The median RFS (D), OS (E) and CSS (F) after resection for pCCA were 52 months, 65 months and 50 months for the CC/CA genotype and 15 months, 19 months, 14 months for the AA genotype. iCCA: Intrahepatic cholangiocarcinoma; pCCA: Perihilar cholangiocarcinoma.

study was designed as an exploratory analysis in a relatively rare disease setting, formal correction for multiple comparisons was not applied in order to avoid excessive type II error. Importantly, the association between *ARID5B* rs10740055 and survival outcomes remained consistent in multivariable models and sensitivity analyses (Supplementary Table 9), supporting the robustness of this finding. Nonetheless, the results should be interpreted cautiously and require validation in independent cohorts.

The present study represents a retrospective single-center analysis, which may limit the generalizability of the findings. Although the cohort was well characterized and derived from a high-volume hepatobiliary center, external validation in independent patient populations will be essential before these germline polymorphisms can be considered for clinical risk stratification. Future multicenter studies and prospective investigations will be necessary to confirm the prognostic relevance of *ARID5B* and *LEPR* variants and to determine whether incorporation of host genetic markers can improve existing prognostic models for CCA.

Given the limited sample size inherent to rare malignancies, model complexity was deliberately restricted. The number of EPV in the multivariable Cox models was within accepted methodological ranges (Supplementary Table 8). Sensitivity analyses using reduced models yielded comparable effect estimates (Supplementary Table 9), supporting model stability. However, independent validation in external cohorts remains necessary. Given the candidate-gene design and limited sample size inherent to rare malignancies, no global multiplicity correction was applied. Therefore, the reported associations should be interpreted as hypothesis-generating and require independent validation. Although germline DNA was extracted from FFPE-derived non-tumor tissue, which may be associated with DNA fragmentation, the use of validated genotyping assays and strict quality control measures supports the reliability of the genotyping results.

## CONCLUSION

Looking forward, our findings should be validated and extended in larger, multi-center studies. Conducting a collaborative analysis across multiple institutions or ethnic groups would help confirm whether *ARID5B* and *LEPR* polymorphisms consistently stratify risk and would refine the estimated magnitude of their effect. In line with this, a recent systematic review highlighted that more large-scale multicentric investigations are needed to determine the true potential of SNP markers for CCA prognostication.

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## FOOTNOTES

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**Country of origin:** Germany

**Author contributions:** Wang G, Otto C and Bednarsch J designed the study, developed the software, wrote the original draft; Wang G, Lueong SS, Siveke J, Heij L and Bednarsch J were responsible for developing the methodology; Liu D and Al-Masri TM performed the validation; Wang G, Otto C, Liu D, Al-Masri TM, Neumann U, Heij L and Bednarsch J participated in the formal analysis; Wang G, Otto C, Liu D, Al-Masri TM, Lueong SS, Siveke J, Heise D, Meister FA, Vondran FWR, Lurje G, Neumann U, Heij L and Bednarsch J participated in the investigation; Neumann U and Bednarsch J provided the resources; Liu D and Al-Masri TM curated the data; Liu D, Al-Masri TM, Lueong SS, Siveke J, Luedde T, Heise D, Meister FA, Vondran FWR, Lurje G, Neumann U and Heij L participated in the review and editing; Wang G and Otto C performed the visualization; Bednarsch J and Neumann U supervised the study; Heij L and Bednarsch J administered the project; Wang G, Liu D and Bednarsch J acquired the funding; and all authors have read the manuscript and approved the final version.

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