

MRI and Survival in Intrahepatic Cholangiocarcinoma: Does Proximal Bile Duct Dilatation Matter?

Mecit Kantarcı

akkanrad@hotmail.com

Atatürk University

Ayça Seyfettin

Güven Hospital

Sebnem Karasu

Izmir Kâtip Çelebi University

İlkay İdilman

Hacettepe University

Ezgi Güler

Ege University

Ece Özer

Şişli Etfal Eğitim ve Araştırma Hastanesi

Yunus Sür

Izmir Kâtip Çelebi University

Ali Osman Gülmez

Erzincan Binali Yıldırım University

Sıtkı Safa Taflan

Istanbul University

İlhan Hekimsoy

Ege University

Şükrü Mehmet Ertürk

Istanbul University

Muşturay Karçaaltıncaba

Hacettepe University

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Abstract

Purpose

To evaluate the association between pretreatment magnetic resonance imaging (MRI) features and overall survival (OS) in patients with intrahepatic cholangiocarcinoma, and their incremental prognostic value beyond clinical and biochemical parameters.

Methods

In this multicenter retrospective cohort study, 210 patients were screened, and 57 with diagnostic-quality pretreatment liver MRI and available clinical, biochemical, imaging, and follow-up data were included in the OS analysis. Evaluated MRI features included tumor distribution, diffusion restriction, proximal bile duct dilatation, peritoneal dissemination, small-duct/large-duct phenotype, and apparent diffusion coefficient (ADC)-based measurements. OS was analyzed using the Kaplan-Meier method, log-rank test, and Cox regression.

Results

Forty-nine deaths occurred (86.0%); median OS was 14.8 months (95% CI, 7.3–21.2), with 1- and 2-year OS rates of 56.7% and 34.4%, respectively. ADC ratio and mean ADC values were not associated with OS ($p = 0.400$ and $p = 0.735$). Older age, low serum albumin level, high neutrophil-to-lymphocyte ratio, elevated carcinoembryonic antigen, presence of peritoneal dissemination, and large-duct phenotype (HR, 3.18; $p < 0.001$) were associated with OS in univariable analysis. Tumor distribution was not significantly associated with OS ($p = 0.579$). In the multivariable model, low serum albumin level (HR, 15.34; $p < 0.001$), older age (HR, 1.07; $p < 0.001$), and proximal bile duct dilatation (HR, 2.23; $p = 0.029$) remained independently associated with OS.

Conclusion

Proximal bile duct dilatation, an MRI feature suggestive of a large-duct phenotype, was independently associated with OS beyond albumin level and age, whereas tumor distribution was not. This readily assessable feature may complement clinical and biochemical parameters in pretreatment risk stratification, pending validation in larger cohorts.

Introduction

Intrahepatic cholangiocarcinoma is an aggressive primary hepatic malignancy arising from the intrahepatic biliary epithelium between the bile ductules and second-order bile ducts, and represents the second most common primary liver cancer after hepatocellular carcinoma.¹ Its global incidence has

increased over recent decades, and because early-stage disease is often clinically silent, diagnosis is frequently delayed until advanced stages, highlighting the importance of accurate staging, prognostic risk stratification, and multidisciplinary management.²³

Although surgical resection remains the main potentially curative treatment for eligible patients with intrahepatic cholangiocarcinoma, many patients present with advanced-stage disease and long-term survival remains limited.⁴ Therefore, reliable prognostic biomarkers available at diagnosis or before treatment are clinically important for risk stratification, treatment planning, patient counseling, follow-up scheduling, and selection of candidates for clinical trials.² Because many existing staging systems rely primarily on pathological information, there is a continued need for preoperative prognostic indicators integrating clinical, biochemical, and imaging-derived parameters.⁵

Clinical and biochemical parameters are key components of prognostic assessment in intrahepatic cholangiocarcinoma. Serum tumor markers, liver function tests, systemic inflammatory indices, and nutritional parameters have been associated with survival outcomes. In particular, serum albumin provides information on hepatic reserve, systemic inflammation, and nutritional status, whereas the neutrophil-to-lymphocyte ratio represents an easily accessible marker of systemic inflammatory response and has been associated with adverse survival outcomes in intrahepatic cholangiocarcinoma.⁶ However, prognostic assessment based solely on clinical and laboratory variables may not fully capture additional information related to imaging-defined tumor distribution, tumor burden, and biological aggressiveness.⁷

Magnetic resonance imaging (MRI) plays a central role in the diagnosis, local staging, and pretreatment characterization of intrahepatic cholangiocarcinoma.² Beyond conventional anatomic assessment, MRI provides information on tumor distribution, tumor burden, biliary and vascular involvement, enhancement patterns, diffusion restriction, and quantitative apparent diffusion coefficient (ADC) measurements, all of which may reflect tumor aggressiveness and prognosis.⁸ Previous studies have reported associations between imaging features, including multifocality, infiltrative tumor margins, biliary invasion, arterial phase enhancement patterns, and diffusion-related parameters, and survival outcomes in patients with intrahepatic cholangiocarcinoma.^{7–9}

Nevertheless, the complementary prognostic role of MRI features when integrated with readily available clinical and biochemical parameters remains incompletely defined. This distinction is clinically relevant, because the utility of imaging biomarkers depends not only on their association with survival in isolation, but also on whether they provide independent or incremental prognostic information beyond established clinical and laboratory variables. This study aimed to evaluate the association between pretreatment MRI features and overall survival (OS) in patients with intrahepatic cholangiocarcinoma, and to identify which clinical, biochemical, and imaging variables remain independently associated with survival in a multivariable model. We further characterized this association through a prognostic risk score with internal validation and through analysis of survival duration among patients who died, in order to

distinguish features associated with the overall probability of death from those associated with the pace of clinical decline.

Materials and Methods

Study Design and Patient Population

Patients diagnosed with intrahepatic cholangiocarcinoma at five different centers between May 2016 and May 2026 were retrospectively reviewed. Eligible patients were required to have a diagnostic-quality pretreatment liver MRI examination and available clinical, biochemical, imaging, and follow-up data. Data was obtained from institutional electronic medical records, radiology archives, laboratory information systems, pathology reports, and follow-up records.

The initial cohort consisted of 210 patients diagnosed with intrahepatic cholangiocarcinoma. Patients aged 18 years or older were included if they had a diagnosis of intrahepatic cholangiocarcinoma based on histopathologic confirmation or compatible clinic-radiologic findings, had undergone pretreatment liver MRI, and had sufficient follow-up information for OS analysis. Patients were excluded if they had no pretreatment MRI examination, inadequate MRI quality for radiologic evaluation, missing or unreliable survival data, or a negative or inconsistent interval between the MRI date and the date of death or last follow-up; patients with a synchronous second primary malignancy that could independently affect survival were also excluded. After applying these criteria, 72 patients remained eligible; of these, 15 were further excluded because the tumor was ultimately classified as perihilar (hilar) cholangiocarcinoma rather than strictly intrahepatic cholangiocarcinoma, to maintain a diagnostically homogeneous cohort, yielding a final eligible cohort of 57 patients (Fig. 1). OS analyses were performed in these 57 patients; the number of patients included in individual variable-based analyses varied according to data availability. During follow-up, 49 deaths were observed.

Clinical and Biochemical Variables

Clinical variables included age, sex, cholangiocarcinoma subtype, risk factor status, treatment information, available pathologic findings, recurrence status, MRI date, date of death, and date of last follow-up.

Biochemical parameters included serum carbohydrate antigen 19 – 9 (CA 19 – 9), carcinoembryonic antigen (CEA), total bilirubin, direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, international normalized ratio (INR), C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR). Laboratory values closest to the MRI date were used for analysis. Biochemical variables were categorized according to the reference ranges of the respective institutional laboratories. Serum albumin was classified as normal or low. The neutrophil-to-lymphocyte ratio was categorized using a threshold of 3.0, with values ≥ 3.0 defined as high NLR and values < 3.0 defined as low NLR.

MRI Acquisition and Image Analysis

Pretreatment liver MRI examinations were retrospectively retrieved from the radiology archives of the participating centers. MRI examinations were performed using 1.5-T or 3.0-T scanners equipped with phased-array body coils according to standardized institutional liver MRI protocols. The imaging protocol included axial T1-weighted in-phase and opposed-phase gradient-echo sequences, axial and coronal T2-weighted fast spin-echo sequences with and without fat suppression, diffusion-weighted imaging (DWI) with corresponding apparent diffusion coefficient (ADC) maps, and magnetic resonance cholangiopancreatography (MRCP). Dynamic contrast-enhanced imaging was performed after intravenous administration of a hepatobiliary-specific gadolinium-based contrast agent and included precontrast, late arterial, portal venous, transitional, and hepatobiliary phases.

Images were acquired with a slice thickness of 4–6 mm, an interslice gap of 0–1 mm, and a field of view (FOV) of approximately 320–400 mm, adjusted according to patient body habitus. DWI was obtained in the axial plane using multiple b values (0, 50, 400, and 800 s/mm² or equivalent vendor-specific values). ADC maps were automatically generated on the scanner workstation. Breath-hold acquisition was used whenever feasible for T1-weighted dynamic imaging, whereas respiratory-triggered or free-breathing techniques were used for T2-weighted and diffusion-weighted sequences according to institutional protocols. MRI protocols were harmonized across participating centers to ensure comparable image quality despite minor vendor-specific variations.

The evaluated MRI features included tumor distribution, maximum tumor diameter, tumor morphology, mass-forming configuration, T1 signal characteristics, presence of necrosis, hemorrhage, capsular retraction, progressive central enhancement, persistent delayed enhancement, washout-like appearance, diffusion restriction, suspected peritoneal dissemination, regional lymph node involvement, proximal bile duct dilatation, unilateral or bilateral biliary involvement, imaging phenotype suggestive of small-duct or large-duct type intrahepatic cholangiocarcinoma, mean ADC value, and ADC ratio.

Tumor distribution was categorized as solitary or multifocal. In multifocal disease, the dominant lesion was defined as the largest measurable intrahepatic lesion and was used for maximum diameter and ADC-based quantitative measurements. Maximum tumor diameter was measured on the sequence on which the margins of the lesion were most conspicuous. Diffusion restriction was defined as visually high signal intensity on high-b-value DWI with corresponding low signal intensity on ADC maps.

Mean ADC values were obtained by placing a representative round or oval region of interest (ROI) within the solid, non-necrotic, and most diffusion-restricted portion of the dominant tumor. Areas of necrosis, cystic change, hemorrhage, bile ducts, large vascular structures, visible artifacts, and peritumoral non-tumoral parenchymal changes were avoided whenever possible. For larger lesions, an ROI of approximately 1–2 cm² was used; for smaller lesions, the largest possible ROI confined to the solid tumor component was placed. The ADC ratio was calculated as the ratio of the tumor mean ADC value to the mean ADC value of the reference liver parenchyma. The reference liver ROI was placed in tumor-free liver parenchyma, preferably in the same hepatic lobe as the lesion; when this was not feasible, the

contralateral lobe was used. Vessels, bile ducts, liver capsule, perfusion abnormalities, atrophic parenchyma, and areas adjacent to the tumor were avoided during reference ROI placement.

The imaging phenotype suggestive of small-duct or large-duct type intrahepatic cholangiocarcinoma was assessed on MRI because histopathologic subtype classification was not uniformly available. A small-duct-type imaging phenotype was considered in peripheral mass-forming tumors without major bile duct involvement or proximal biliary dilatation. A large-duct-type imaging phenotype was considered in tumors with a central, perihepatic-duct intrahepatic location or growth along the major intrahepatic bile ducts, ductal wall thickening, proximal biliary dilatation, periductal infiltrating pattern, lobar atrophy, or major bile duct involvement.

Washout-like appearance was defined as a component showing arterial phase enhancement that became relatively hypointense compared with the surrounding liver parenchyma on the portal venous phase, with or without delayed phase assessment. In examinations performed with hepatobiliary contrast agents, hepatobiliary phase hypointensity alone was not considered washout-like appearance.

Regional lymph nodes were considered suspicious when the short-axis diameter was ≥ 10 mm or when morphologic features suggestive of malignancy were present, including round shape, loss of fatty hilum, irregular margins, heterogeneous enhancement, central necrosis, diffusion restriction, or clustering of multiple nodes in the same nodal station.

MRI examinations were evaluated by consensus at each center by two radiologists experienced in abdominal imaging, one of whom was a senior radiologist. Readers were blinded to survival outcomes and follow-up data at the time of image evaluation.

Outcome

The primary outcome was OS. OS was defined as the interval between the MRI date and the date of death or last follow-up. Patients who died during follow-up were considered to have experienced an event, whereas patients alive at the last follow-up were censored. Survival time was calculated in days.

Statistical Analysis

Statistical analyses were performed using Python (version 3.12) with the pandas, lifelines, SciPy, and NumPy packages. Normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were summarized as mean $\pm$ standard deviation when normally distributed and as median with interquartile range when non-normally distributed; categorical variables were presented as counts and percentages.

OS was estimated using the Kaplan–Meier method, with median OS and restricted mean survival time (60-month horizon) reported given that the survival curve did not reach zero within the observation period. Univariable Cox proportional hazards regression was used to evaluate associations between

clinical, biochemical, and MRI variables and OS, with hazard ratios, 95% confidence intervals, and p values calculated for each.

Variables associated with OS at $p < 0.10$ in univariable analyses, together with clinically relevant variables, were considered candidates for multivariable Cox regression; the final three-covariate model (albumin status, age, and proximal bile duct dilatation) was selected based on statistical performance, preservation of sample size, and clinical relevance, following an events-per-variable heuristic of approximately 10 events per covariate.

The proportional hazards assumption was assessed using Schoenfeld residuals and graphical diagnostic methods.

Additional analyses — including comparison of baseline characteristics by vital status, Kaplan–Meier analysis of the dichotomized ADC ratio, detailed multivariable model-selection procedures, evaluation of further qualitative MRI features, construction of a prognostic risk score with internal cross-validation, and analysis of survival duration among patients with a documented death — are detailed in the Supplementary Methods. All statistical tests were two-sided, and a p value of < 0.05 was considered statistically significant.

Ethics Approval

This retrospective study was approved by the Erzincan Binali Yıldırım University Institutional Review Board/Ethics Committee. Due to the retrospective design of the study, a waiver for obtaining informed consent was granted. The ethics committee approval number was 2023-13/7, and the approval date was June 22, 2023. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Patient Cohort and Survival Outcomes

Of the 210 patients initially screened, 57 met all inclusion and exclusion criteria and were included in the final overall survival analysis. During follow-up, 49 deaths were observed (86.0%), whereas 8 patients (14.0%) were censored at the date of last follow-up. The mean age of the study cohort was 65.3 ± 10.2 years, and the median age was 66 years (IQR, 57–74). The median maximum diameter of the dominant lesion was 68.6 mm (IQR, 40.0–98.0). The median ADC ratio was 0.81 (IQR, 0.71–0.99). Baseline clinical, biochemical, and MRI characteristics of the cohort, overall and stratified by vital status, are summarized in Table 1. Patients who died during follow-up were significantly older than those who were alive or censored (median 68 versus 58 years; $p = 0.011$) and were more likely to have proximal bile duct dilatation (73.5% versus 25.0%; $p = 0.013$). In addition, deceased patients more frequently exhibited elevated laboratory parameters, including ALP (53.1% versus 0.0%; $p = 0.006$), AST (53.1% versus 0.0%; $p = 0.006$), GGT (75.5% versus 0.0%; $p < 0.001$), and a high NLR (51.2% versus 0.0%; $p = 0.026$). Kaplan–Meier analysis demonstrated a progressive decline in OS during follow-up, with a marked decrease in

survival probability in the early period after pretreatment MRI assessment (Fig. 2). Median OS was 14.8 months (95% CI, 7.3–21.2). Because the Kaplan–Meier curve did not reach zero within the observation period, mean OS was additionally summarized as the restricted mean survival time truncated at a 60-month horizon, which was 21.6 months. The 1-year and 2-year OS rates were 56.7% and 34.4%, respectively.

Table 1

Baseline clinical, biochemical, and MRI characteristics of the study cohort, overall and by vital status (n = 57)

Characteristic	Overall (n = 57)	Deceased (n = 49)	Alive/Censored (n = 8)	p
Clinical				
Age, mean $\pm$ SD, years	65.3 $\pm$ 10.2	66.6 $\pm$ 10.3	57.2 $\pm$ 4.3	0.011
Sex, female	31 (54.4%)	27 (55.1%)	4 (50.0%)	1.000
Sex, male	26 (45.6%)	22 (44.9%)	4 (50.0%)	
Follow-up duration, median (IQR), months	11.5 (3.6–25.9)	12.4 (3.6–25.5)	11.4 (7.2–40.3)	0.654
MRI-Derived Imaging Features				
Maximum tumor diameter, median (IQR), mm	68.6 (40.0–98.0)	65.5 (40.0–100.0)	75.8 (35.3–83.5)	0.558
Tumor distribution, solitary	30 (52.6%)	24 (49.0%)	6 (75.0%)	0.258
Tumor distribution, multifocal	27 (47.4%)	25 (51.0%)	2 (25.0%)	
Diffusion restriction	53 (93.0%)	45 (91.8%)	8 (100.0%)	1.000
Suspected peritoneal dissemination	15 (26.3%)	15 (30.6%)	0 (0.0%)	0.095
Proximal bile duct dilatation	38 (66.7%)	36 (73.5%)	2 (25.0%)	0.013
Imaging phenotype, large-duct type	22/55 (40.0%)	22/47 (46.8%)	0/8 (0.0%)	0.016
ADC ratio, median (IQR)	0.81 (0.71–0.99)	0.81 (0.68–1.02)	0.81 (0.80–0.83)	0.845
Median (IQR) of mean ADC value, $\times 10^{-3}$ mm ² /s	0.92 (0.74–1.00)	0.91 (0.72–1.01)	0.94 (0.89–0.96)	0.543
Biochemical Parameters				
Albumin (< 3.5 g/dL)	7 (12.3%)	7 (14.3%)	0 (0.0%)	0.577
Neutrophil-to-lymphocyte ratio ($\geq$ 3.0)	21/47 (44.7%)	21/41 (51.2%)	0/6 (0.0%)	0.026
CRP (> 5 mg/L)	40 (70.2%)	35 (71.4%)	5 (62.5%)	0.684
CEA (> 5 ng/mL)	12/55 (21.8%)	12/47 (25.5%)	0/8 (0.0%)	0.178
CA 19 – 9 (> 37 U/mL)	30/55 (54.5%)	27/47 (57.4%)	3/8 (37.5%)	0.446

Characteristic	Overall (n = 57)	Deceased (n = 49)	Alive/Censored (n = 8)	p
Clinical				
Total bilirubin (> 1.2 mg/dL)	7 (12.3%)	7 (14.3%)	0 (0.0%)	0.577
Direct bilirubin (> 0.3 mg/dL)	12 (21.1%)	12 (24.5%)	0 (0.0%)	0.182
ALP (> 130 U/L)	26 (45.6%)	26 (53.1%)	0 (0.0%)	0.006
GGT (> 55 U/L)	37 (64.9%)	37 (75.5%)	0 (0.0%)	< 0.001
AST (> 40 U/L)	26 (45.6%)	26 (53.1%)	0 (0.0%)	0.006
ALT (> 41 U/L)	14 (24.6%)	14 (28.6%)	0 (0.0%)	0.179
INR (> 1.2)	10 (17.5%)	10 (20.4%)	0 (0.0%)	0.327

IQR, interquartile range; ADC, apparent diffusion coefficient; CRP, C-reactive protein; CEA, carcinoembryonic antigen; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio. p values were derived using the Mann-Whitney U test for continuous variables (associated with the median [IQR] row) and Fisher's exact test for categorical variables, comparing deceased versus alive/censored patients; p values are shown once per variable and omitted for redundant category rows (-).

Univariable Cox Regression Analysis

In univariable Cox proportional hazards regression analysis, several clinical, biochemical, and MRI-derived variables were associated with OS. Among clinical and biochemical parameters, older age (HR, 1.04 per year; 95% CI, 1.01–1.07; $p = 0.010$), low serum albumin level (< 3.5 g/dL; HR, 3.96; 95% CI, 1.68–9.36; $p = 0.002$), high NLR (≥ 3.0 ; HR, 2.86; 95% CI, 1.43–5.73; $p = 0.003$), and elevated CEA level (> 5 ng/mL; HR, 3.92; 95% CI, 1.84–8.34; $p < 0.001$) were associated with worse OS. Elevated CRP (> 5 mg/L), GGT (> 55 U/L), and total bilirubin (TBil; >1.2 mg/dL) showed borderline associations with mortality ($0.05 < p < 0.11$) but did not reach statistical significance. Detailed results of the univariable Cox regression analyses are presented in Table 2. Several additional qualitative MRI features were also explored in exploratory analyses; none were significantly associated with OS (Supplementary Table 1).

Table 2
Univariable Cox proportional hazards regression analysis of factors associated with overall survival

Variable	HR (95% CI)	p
Clinical		
Age, per year	1.04 (1.01–1.07)	0.010
Biochemical		
Albumin, < 3.5 g/dL vs normal	3.96 (1.68–9.36)	0.002
NLR, ≥ 3.0 vs < 3.0	2.86 (1.43–5.73)	0.003
CEA, > 5 ng/mL vs normal	3.92 (1.84–8.34)	< 0.001
CRP, > 5 mg/L vs normal	1.78 (0.94–3.39)	0.077
GGT, > 55 U/L vs normal	1.76 (0.90–3.44)	0.100
Total bilirubin, > 1.2 mg/dL vs normal	1.96 (0.87–4.41)	0.105
ALP, > 130 U/L vs normal	1.42 (0.80–2.54)	0.231
AST, > 40 U/L vs normal	1.40 (0.79–2.50)	0.249
INR, > 1.2 vs normal	0.66 (0.30–1.43)	0.290
CA 19 – 9, > 37 U/mL vs normal/low	1.23 (0.67–2.25)	0.510
Direct bilirubin, > 0.3 mg/dL vs normal	0.80 (0.39–1.65)	0.550
ALT, > 41 U/L vs normal	0.89 (0.46–1.74)	0.732
MRI-Derived Imaging Features		
Suspected peritoneal dissemination, present vs absent	3.15 (1.61–6.17)	0.001
Imaging phenotype, large-duct vs small-duct type	3.18 (1.60–6.33)	< 0.001
Proximal bile duct dilatation, present vs absent	1.83 (0.95–3.52)	0.072
Maximum tumor diameter, per mm	1.01 (1.00–1.01)	0.138
Diffusion restriction, present vs absent	0.45 (0.15–1.30)	0.141
Tumor distribution, multifocal vs solitary	1.18 (0.66–2.10)	0.579
ADC mean, continuous	1.25 (0.31–5.04)	0.752
ADC ratio, continuous	0.99 (0.25–4.02)	0.993

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; AST,

aspartate aminotransferase; INR, international normalized ratio; ALT, alanine aminotransferase; ADC, apparent diffusion coefficient.

Among MRI-derived variables, the imaging phenotype suggestive of large-duct type intrahepatic cholangiocarcinoma (Fig. 3) was strongly associated with worse OS (HR, 3.18; 95% CI, 1.60–6.33; $p < 0.001$), and suspected peritoneal dissemination was associated with a higher mortality risk (HR, 3.15; 95% CI, 1.61–6.17; $p = 0.001$) (Fig. 4). Proximal bile duct dilatation showed a borderline association with worse OS (HR, 1.83; 95% CI, 0.95–3.52; $p = 0.072$). Because large-duct phenotype was present only in tumors with proximal bile duct dilatation, these two closely related features were not entered into the multivariable model simultaneously, to avoid collinearity. In contrast, tumor distribution (multifocal versus solitary) was not significantly associated with OS (HR, 1.18; 95% CI, 0.66–2.10; $p = 0.579$), nor were diffusion restriction ($p = 0.141$), maximum tumor diameter ($p = 0.138$), or ADC ratio and mean ADC as continuous variables ($p = 0.993$ and $p = 0.752$, respectively). When dichotomized at the median, ADC ratio and mean ADC were similarly not associated with OS on log-rank testing ($p = 0.400$ and $p = 0.735$, respectively).

Multivariable Cox Regression Analysis

In the final multivariable Cox proportional hazards regression model, low serum albumin (< 3.5 g/dL), older age, and proximal bile duct dilatation remained independently associated with OS (Fig. 5, Table 3). Low serum albumin was independently associated with a substantially increased risk of death (HR, 15.34; 95% CI, 5.09–46.24; $p < 0.001$). Older age was independently associated with increased mortality risk (HR, 1.07 per year; 95% CI, 1.04–1.10; $p < 0.001$). The presence of proximal bile duct dilatation, an MRI feature suggestive of a large-duct or central biliary phenotype, was an independent unfavorable prognostic feature (HR, 2.23; 95% CI, 1.09–4.58; $p = 0.029$) (Fig. 6). The model showed a concordance index of 0.728. Because proximal bile duct dilatation and the directly assessed large-duct imaging phenotype were highly correlated, an alternative model substituting the large-duct phenotype for proximal bile duct dilatation was also evaluated; this model yielded materially similar findings (albumin HR, 10.64; age HR, 1.06; large-duct phenotype HR, 2.07; $p = 0.043$) but with a lower concordance index (0.712). Proximal bile duct dilatation was therefore retained in the primary model, with the large-duct phenotype analysis serving as confirmatory evidence.

Table 3
Final multivariable Cox proportional hazards regression model for overall survival

Variable	HR (95% CI)	p
Albumin, low vs normal	15.34 (5.09–46.24)	< 0.001
Age, per year	1.07 (1.04–1.10)	< 0.001
Proximal bile duct dilatation, present vs absent	2.23 (1.09–4.58)	0.029

HR, hazard ratio; CI, confidence interval. Model derived from N = 57 patients with 49 events; concordance index = 0.728. No violation of the proportional hazards' assumption was identified for any covariate (Schoenfeld residuals, all $p > 0.05$).

These findings suggest that MRI-derived proximal bile duct dilatation may provide prognostic information independent of routinely available clinical and biochemical parameters. In contrast, tumor distribution was not independently associated with OS in the multivariable model.

Proportional Hazards Assumption

The proportional hazards assumption was assessed for variables included in the final multivariable model (albumin status, age, and proximal bile duct dilatation) using scaled Schoenfeld residuals and graphical diagnostic methods. No relevant violation was identified for any covariate (all $p > 0.05$). Exploratory diagnostics for ADC ratio also showed no evidence of a significant time-dependent effect.

Prognostic Risk Score and Internal Validation

To illustrate the combined prognostic value of the final multivariable model, a linear prognostic index was calculated for each patient as a weighted sum of albumin status, age, and proximal bile duct dilatation, using the corresponding regression coefficients. Patients were stratified into tertiles of this index, defining low-, intermediate-, and high-risk groups ($n = 19$ each). OS differed markedly across risk groups (multivariate log-rank $p < 0.001$; Fig. 7): median OS was 52.5 months in the low-risk group, compared with 7.3 and 7.4 months in the intermediate- and high-risk groups, respectively. Internal validation of the final multivariable model using 5-fold cross-validation yielded a mean concordance index of 0.78 (SD, 0.07; range, 0.69–0.89) across folds, compared with an apparent (in-sample) concordance index of 0.73 (0.73 with mild penalization), indicating reasonable internal discriminative performance given the sample size. Formal external validation in an independent cohort was not performed and remains an important direction for future research.

Factors Associated with Time-to-Death Among Decedents

Among the 49 patients with a documented death, for whom the exact interval between MRI and death was known, we examined survival duration directly. This analysis addresses a distinct question from the Cox regression models above: whether a feature is associated with a shorter time-to-death once death occurs, rather than with the eventual occurrence of death itself. Low serum albumin level (median, 3.1 versus 13.4 months; $p = 0.023$), suspected peritoneal dissemination (median, 5.3 versus 17.6 months; $p = 0.037$), and arterial phase peripheral rim enhancement (median, 6.4 versus 24.1 months; $p = 0.048$) were associated with markedly shorter survival duration among patients who died (Table 4). In contrast, proximal bile duct dilatation, the primary independent MRI predictor identified in the multivariable model, was not associated with survival duration among decedents ($p = 0.564$), nor was the large-duct imaging phenotype ($p = 0.107$), tumor distribution ($p = 0.596$), or diffusion restriction ($p = 0.622$). Age, tumor diameter, ADC ratio, and mean ADC were also not significantly correlated with survival duration among decedents (Spearman $p > 0.2$ for all).

Table 4
Association Between Key Clinical and Imaging Features and Duration of Survival Among Patients Who Died (n = 49)

Feature	Median OS, Feature Present, months (n)	Median OS, Feature Absent, months (n)	p
Albumin, low vs normal	3.1 (7)	13.4 (42)	0.023
Suspected peritoneal dissemination, present vs absent	5.3 (15)	17.6 (34)	0.037
Arterial phase peripheral rim enhancement, present vs absent [‡]	6.4 (27)	24.1 (20)	0.048
Large-duct imaging phenotype, present vs absent [‡]	10.3 (22)	9.4 (25)	0.107
Proximal bile duct dilatation, present vs absent	12.8 (36)	5.5 (13)	0.564
Tumor distribution, multifocal vs solitary	8.1 (25)	14.4 (24)	0.596
Diffusion restriction, present vs absent	13.5 (45)	7.8 (4)	0.622

OS, overall survival. p values were derived using the Mann-Whitney U test comparing survival duration between feature-positive and feature-negative patients among those who died. [‡]Available in 47/49 deceased patients. [‡]Available in 47/49 deceased patients in whom arterial phase enhancement pattern was assessable.

Discussion

In this multicenter retrospective cohort study, we assessed the prognostic significance of pretreatment MRI features in patients with intrahepatic cholangiocarcinoma, in conjunction with clinical and biochemical parameters. The principal finding was that proximal bile duct dilatation, albumin status, and age were each independently associated with overall survival within the same final multivariable Cox regression model, with bile duct dilatation associated with more than a two-fold increase in mortality risk. Among all evaluated MRI variables, proximal bile duct dilatation was the only imaging feature that remained significant alongside these clinical and biochemical factors. A complementary analysis restricted to patients with a documented death further indicated that low albumin, suspected peritoneal dissemination, and arterial phase peripheral rim enhancement were each associated with a markedly shorter interval between MRI and death, whereas proximal bile duct dilatation was not, suggesting that these features may reflect distinct aspects of disease biology — namely, the pace of terminal decline versus the overall probability of death.

This finding is consistent with the biological distinction between small-duct and large-duct subtypes of intrahepatic cholangiocarcinoma. In the fifth-edition World Health Organization classification, these

subtypes are histopathologically and molecularly distinct, with the large-duct subtype arising from larger, centrally located bile ducts and generally following a more aggressive course.^{17,18} MRI features suggestive of the large-duct phenotype, including proximal biliary dilatation and periductal infiltrative growth, have previously been shown to predict large-duct histology and correlate with survival after resection.¹⁷ A multicenter ultrasound study similarly found that a biliary phenotype based on bile duct dilatation was enriched for large-duct histology and microvascular invasion and was associated with worse survival than a parenchymal phenotype.²⁴ MRI-based studies have also identified intrahepatic duct dilatation as an independent predictor of microvascular invasion.²³ These observations support a plausible biological basis for our finding, suggesting proximal bile duct dilatation may serve as a noninvasive surrogate for a more aggressive, large-duct-type phenotype.

This rationale is directly supported by our own data: radiologists classified tumors by consensus as small-duct or large-duct type based on predefined MRI criteria, and this large-duct phenotype was strongly associated with OS (HR, 3.18; 95% CI, 1.60–6.33; $p < 0.001$). All large-duct-type tumors also had proximal bile duct dilatation, whereas fewer than half of small-duct-type tumors did. This internal concordance reinforces that proximal bile duct dilatation captures large-duct phenotype information rather than representing a spurious association.

Analysis restricted to decedents offered further insight into how proximal bile duct dilatation may exert its effect. Low albumin, suspected peritoneal dissemination, and arterial phase peripheral rim enhancement were each associated with a markedly shorter interval between MRI and death, consistent with markers of imminent decline, whereas proximal bile duct dilatation showed no such association. The association between arterial phase peripheral rim enhancement and more rapid decline is consistent with prior work by Min et al., who reported that this enhancement pattern, reflecting a hypovascular, fibrotic tumor phenotype, was associated with worse prognosis in mass-forming intrahepatic cholangiocarcinoma.⁹ This suggests proximal bile duct dilatation may act primarily by increasing the overall probability of death, for example through its association with a less resectable large-duct phenotype, rather than by accelerating the terminal course. Features predicting shorter time-to-death may therefore be more useful for identifying imminent deterioration, whereas proximal bile duct dilatation may better inform earlier pretreatment risk stratification.

Beyond proximal bile duct dilatation, suspected peritoneal dissemination showed the strongest univariable association with OS, plausibly reflecting trans coelomic spread and advanced, unresectable disease.^{12,13} Diffusion restriction, present in most tumors in this cohort, showed only a weak, non-significant association, likely reflecting its near-universal presence. These findings suggest MRI may provide prognostic information across several domains – ductal phenotype, extrahepatic spread, and diffusion-related cellularity – even though not all features retained independent significance after adjustment.

Diffusion-weighted MRI and ADC-derived metrics have also been linked to prognosis in intrahepatic cholangiocarcinoma in several prior reports. Yamada et al. reported an association between lower ADC

values and worse survival, whereas Hokkoku et al. demonstrated that ADC values may predict high Ki-67 expression, supporting a potential relationship with aggressive tumor biology, whereas Sheng et al. reported an association between ADC and early progression in unresectable disease.^{14–16} In contrast, ADC-based variables did not retain independent significance in our multivariable model. This discrepancy may reflect differences in patient selection (our cohort was not restricted to resectable or unresectable disease), ADC measurement methodology, or the relatively modest sample size available for these comparisons, which may have limited power to detect a modest independent effect.

In contrast to some prior reports, tumor distribution (solitary versus multifocal) was not independently associated with OS here, illustrating how estimates for imaging biomarkers can be sensitive to sample size and cohort composition. Yoon et al. specifically cautioned that the prognostic value of tumor multiplicity may be underestimated or overestimated depending on the extent of adjustment for other tumor burden-related variables, since multiplicity may act partly through its correlation with these factors rather than through a fully independent pathway.¹¹ Our findings are consistent with this concern: tumor distribution correlated with several other variables in our cohort, which may have attenuated any independent association once bile duct dilatation, albumin, and age were accounted for. This does not exclude a prognostic role for tumor distribution but suggests that, in this cohort, it did not provide incremental information beyond the variables retained in the final model.

Albumin status and age also remained independently associated with OS, consistent with prior evidence that hepatic reserve, nutrition, and host physiology influence outcomes in intrahepatic cholangiocarcinoma.^{19–22} Composite indices combining albumin with inflammatory or coagulation markers, such as the CRP-albumin-lymphocyte index and albumin-to-fibrinogen ratio, may offer incremental value over albumin alone,^{25,26} though these were not evaluated here and represent a promising future direction. These findings support an integrated approach in which MRI characterizes tumor phenotype while laboratory and demographic parameters reflect host physiology.

Clinically, proximal bile duct dilatation can be incorporated into pretreatment MRI assessment without additional sequences or software, potentially helping communicate prognosis-related information consistently across multidisciplinary teams.^{12,13} Emerging radiomics and artificial intelligence approaches applied to the peritumoral bile ducts and parenchyma may eventually offer more granular, reproducible characterization than visual assessment alone.²⁷ Incorporating proximal bile duct dilatation into structured MRI reporting, potentially alongside future radiomics-based refinements, may improve pretreatment risk assessment, although its impact on clinical decision-making requires validation in larger prospective cohorts.

To translate the final model into a form supporting individualized risk assessment, we constructed a linear prognostic index and stratified patients into risk tertiles, which showed clear separation of OS. Five-fold cross-validation suggested reasonable internal discriminative performance, although external validation in an independent cohort remains necessary before clinical use.

Our findings can also be considered alongside existing MRI-based prognostic models for intrahepatic cholangiocarcinoma. Rhee et al. developed an MRI prognostic score in 316 surgically resected patients, incorporating serum CA19-9, tumor multiplicity, lymph node metastasis, and bile duct invasion; this score showed good discrimination in a training set (C-index, 0.738) but weaker performance in an independent validation set (C-index, 0.605), and did not outperform conventional pathological staging systems.⁵ Notably, bile duct invasion was also a component of their model, aligning with our identification of proximal bile duct dilatation as an independent predictor and lending cross-cohort support to the prognostic relevance of ductal involvement in intrahepatic cholangiocarcinoma. However, unlike Rhee et al., we did not find tumor multiplicity to be independently prognostic; this discrepancy may reflect our inclusion of all patients regardless of resectability, whereas Rhee et al. studied a more homogeneous, surgically resected population in whom multiplicity may more directly reflect surgical curability and residual disease burden. Our internally cross-validated concordance index (0.78) was numerically comparable to the training-set performance reported by Rhee et al., although direct comparison is limited by differences in sample size, population, and validation strategy; external validation in an independent cohort remains necessary for both approaches.

This study has several strengths, including an unselected, all-comers population that may enhance generalizability and internal corroboration of proximal bile duct dilatation through an independently assessed imaging phenotype. It further offers a novel distinction between features predicting the overall probability of death versus the pace of terminal decline, and includes internal validation of the final multivariable model through cross-validation and risk-group stratification. Several limitations should also be acknowledged. The retrospective design may have introduced selection bias, and the cohort was relatively limited despite multicenter data collection, which may have reduced power and increased model instability — reflected in the wide confidence interval for albumin status. Follow-up duration varied among censored patients (2.5–58 months), and for those with the shortest follow-up, being alive may partly reflect limited observation time rather than better prognosis. Treatment heterogeneity and differing variable availability may also have influenced results, and ADC measurements may be affected by acquisition parameters and tumor heterogeneity. External validation was not performed, and histopathologic confirmation of small-duct versus large-duct subtype was not uniformly available, so imaging phenotype was used as a surrogate rather than a validated classifier. Future studies should assess whether proximal bile duct dilatation adds value beyond established staging, incorporating pathological and molecular correlation (including FGFR2 and IDH1 status) and external validation.

Conclusion

Proximal bile duct dilatation, an MRI feature suggestive of a large-duct biliary phenotype, was independently associated with overall survival in patients with intrahepatic cholangiocarcinoma, beyond albumin status and age, whereas tumor distribution and ADC-based measurements were not. A complementary analysis further suggested that proximal bile duct dilatation, serum albumin level, presence of peritoneal dissemination, and arterial phase enhancement pattern may capture distinct

aspects of disease biology, ranging from the overall probability of death to the pace of terminal decline. These findings support a role for routinely assessable MRI features in pretreatment risk stratification, best interpreted alongside patient-related factors such as hepatic reserve and age, and should be confirmed in larger, prospectively validated, multicenter cohorts before clinical application.

Declarations

Author Contributions

[MK, II, MK, AOG] contributed to study conception and design. [MK, EG, IH, SK, YS, SSST, SME] performed data acquisition. [MK, EG, IH, SK, YS] performed image analysis. [MK, II, MK, EO, AS, SME] performed statistical analysis. [MK, AOG, AS] drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to institutional and ethical restrictions regarding patient privacy.

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Figures

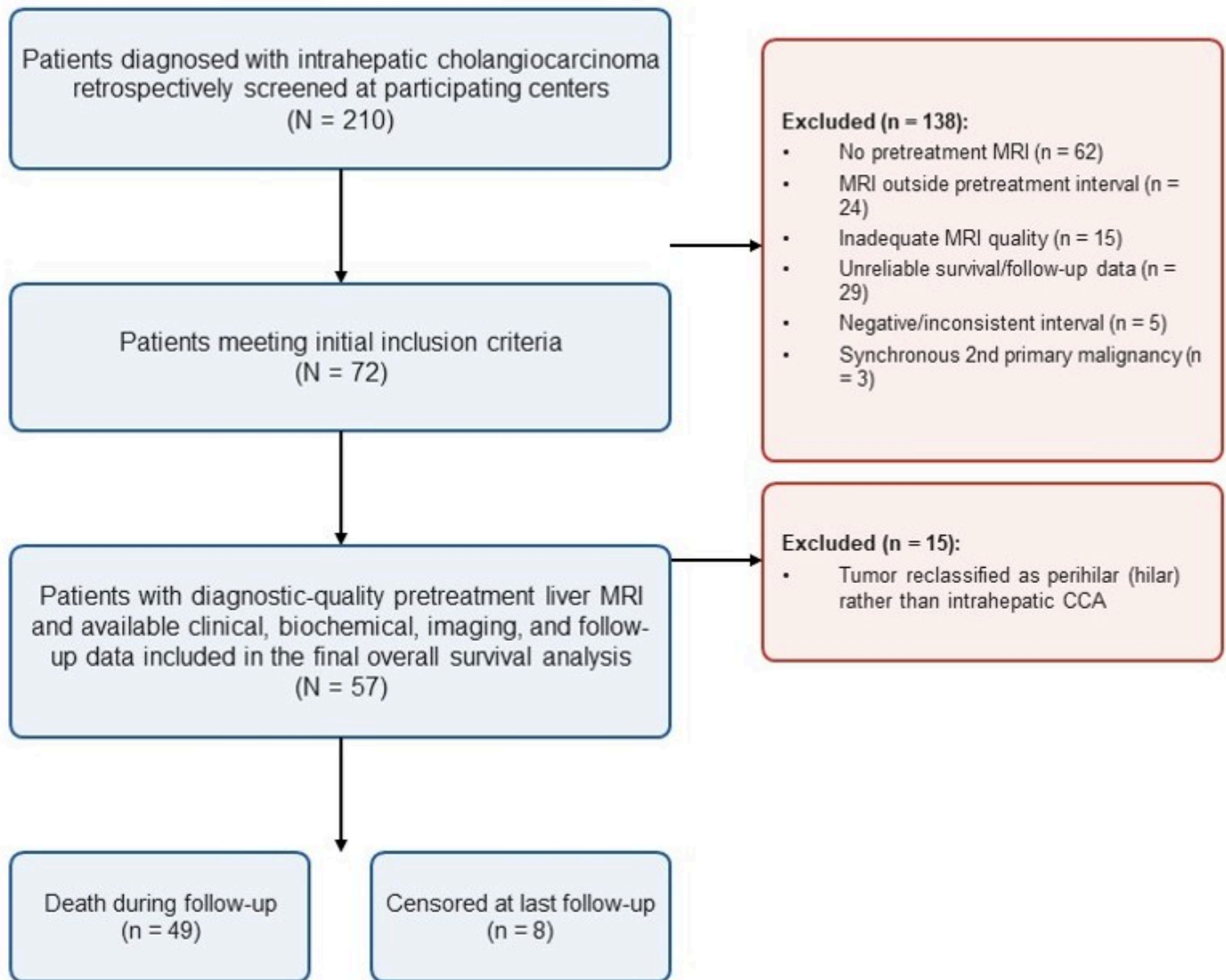


Figure 1

Patient Selection Flowchart for the Overall Survival Analysis

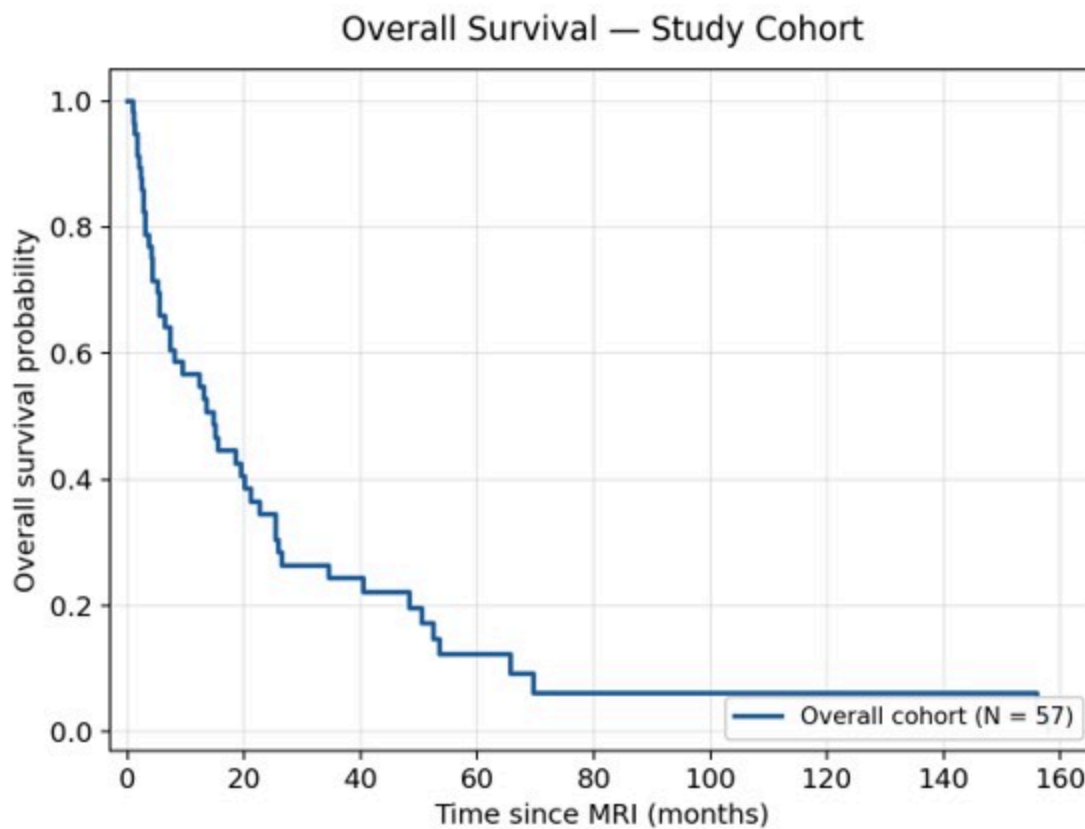


Figure 2

Kaplan–Meier curve of overall survival in the study cohort

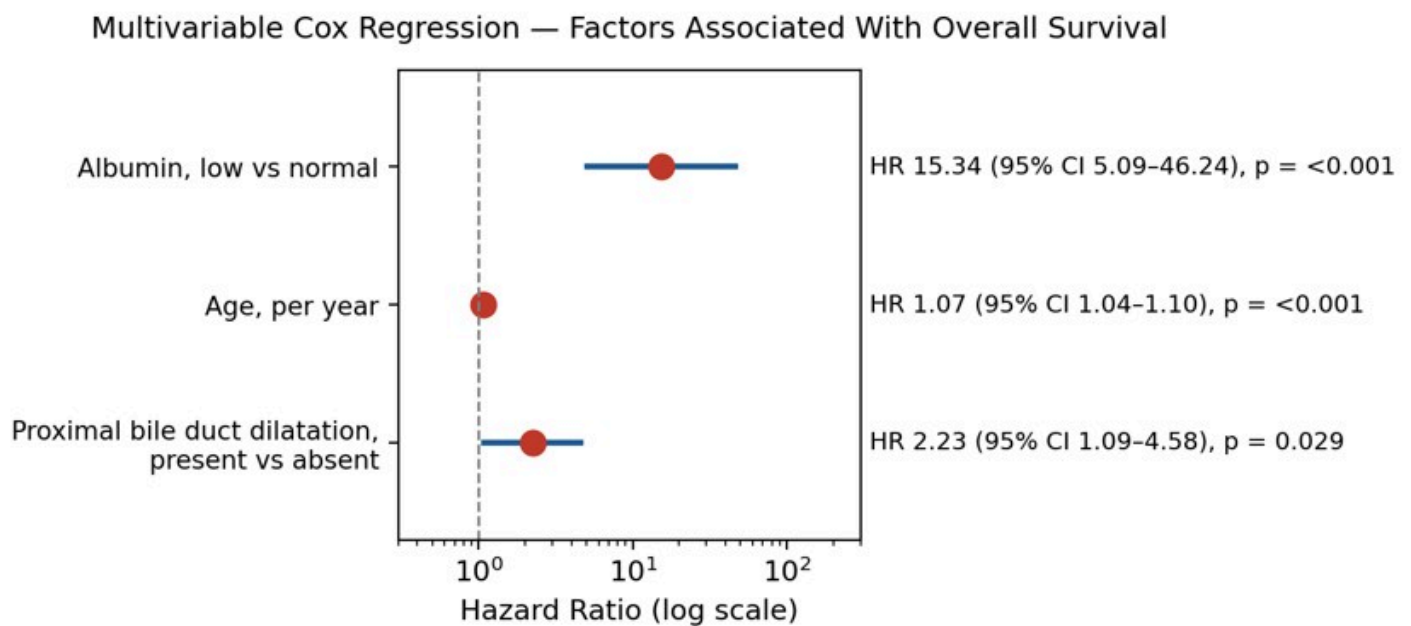


Figure 3

Figure 5. Multivariable Cox regression analysis of factors associated with overall survival

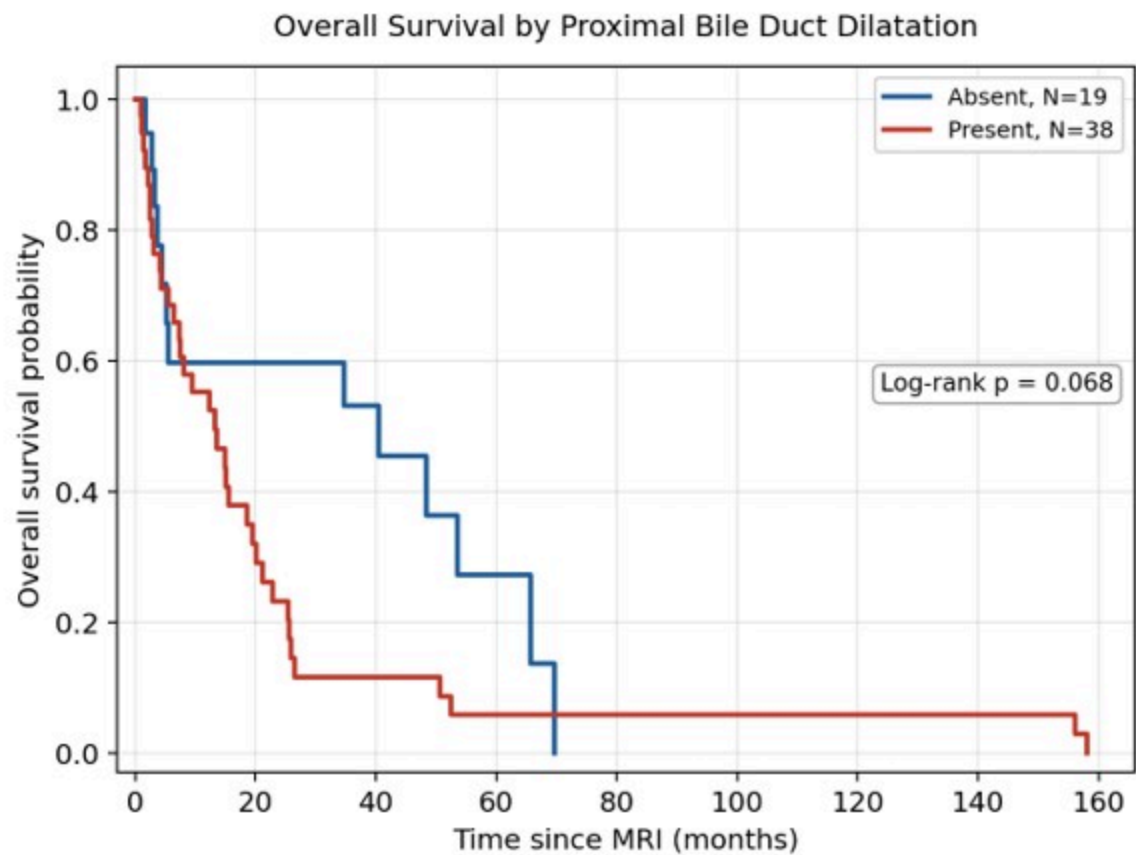


Figure 4

Figure 6. Kaplan–Meier analysis of overall survival according to proximal bile duct dilatation

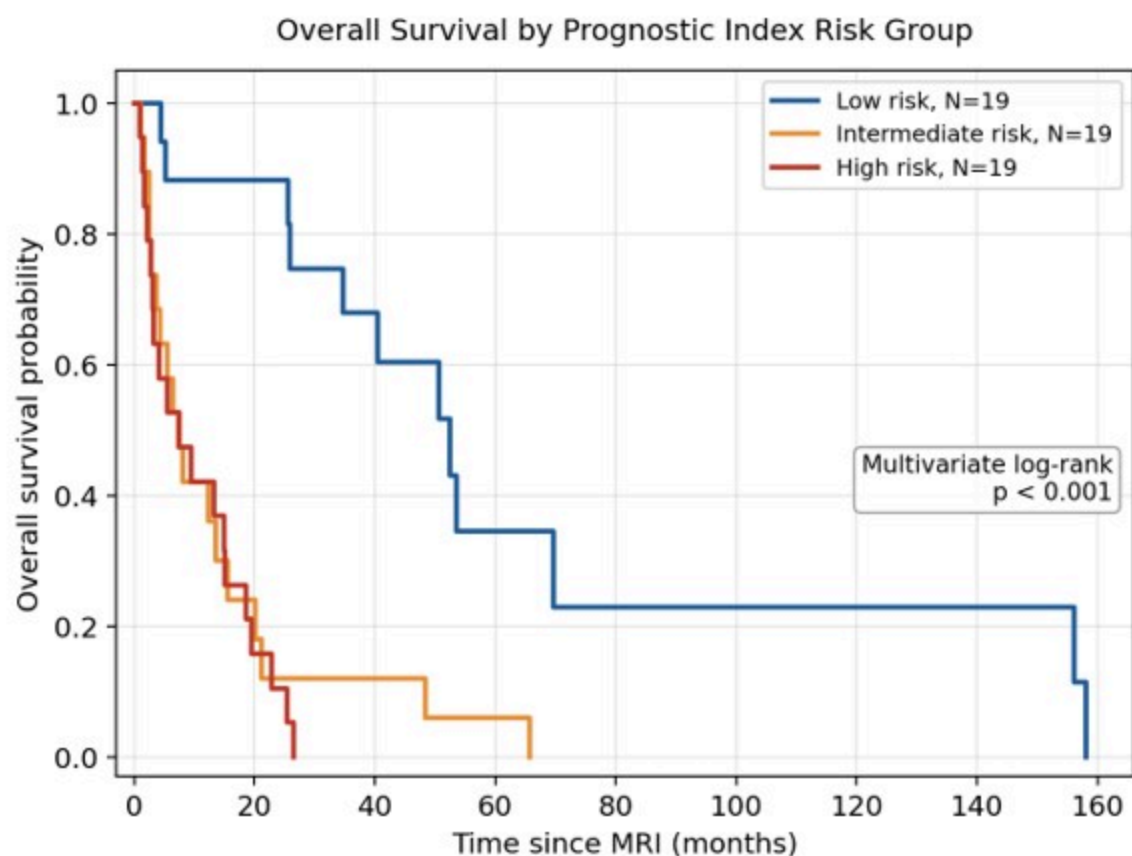


Figure 5

Figure 7. Kaplan–Meier analysis of overall survival by prognostic index risk group (low, intermediate, high)

Supplementary Files

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