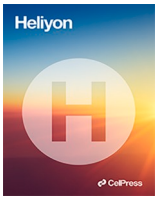
Heliyon 10 (2024) e32113

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Serum high-density lipoprotein cholesterol levels predict early recurrence and prognosis of intrahepatic cholangiocarcinoma after surgical resection

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ARTICLE INFO

Keywords:
Intrahepatic cholangiocarcinoma
Prognosis
Recurrence
Serum high-density lipoprotein cholesterol level

ABSTRACT

Introduction: Dysregulation in lipid metabolism contributes to the occurrence and development of various cancers. The connection between changes in lipid metabolism and the development of intrahepatic cholangiocarcinoma remains uncertain. Our objective was to investigate the significance of blood lipid levels in patients with intrahepatic cholangiocarcinoma who have undergone surgery.

Methods: Ninety-seven ICC patients who underwent surgery were retrospectively enrolled. After 92.2 months of follow-up, the Kaplan-Meier analysis and Cox proportional hazard model were used to calculate overall survival and recurrence-free survival.

Results: The median age of this cohort was 56 years, and 79 (81.4 %) of them were male. Eighty-eight (90.7 %) patients presented with tumor recurrence and 73 (75.3 %) died. In multivariate analyses, high-density lipoprotein cholesterol level ($<$0.91 *vs.* $\geq$ 0.91 mmol/L, hazard ratio [HR] = 2.55; 95 % CI: 1.38–4.71), lymph node metastasis (Yes *vs.* No, HR = 2.58; 95 % CI: 1.28–5.19), etiology factor (chronic HBV infection *vs.* others, HR = 0.5; 95 % CI: 0.28–0.88) and multiple tumor lesions (Yes *vs.* No, HR = 1.85; 95 % CI: 1.01–3.39) were independent predictors of overall survival. However, only high-density lipoprotein cholesterol level (HR = 1.86; 95 % CI: 1.19–2.92) emerged as the independent factor for recurrence-free survival. High-density lipoprotein cholesterol level (HR = 2.07; 95 % CI: 1.26–3.41), etiology factor (HR = 0.49; 95 % CI: 0.29–0.84), and multiple tumor lesions (HR = 2.00; 95 % CI: 1.14–3.51) were independent predictors of early recurrence. For patients who did not experience the spread of cancer to the lymph nodes, there was a significant correlation between the level of high-density lipoprotein cholesterol and their overall survival, recurrence-free survival, and early recurrence. For patients

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https://doi.org/10.1016/j.heliyon.2024.e32113
Received 6 January 2024; Received in revised form 24 May 2024; Accepted 28 May 2024
Available online 29 May 2024

with low pre-operation high-density lipoprotein cholesterol levels, high post-operation high-density lipoprotein cholesterol levels were associated with better prognosis.
Conclusions: Low serum high-density lipoprotein cholesterol level might serve as a sign of poor clinical outcomes (overall survival and recurrence-free survival) and early recurrence among intrahepatic cholangiocarcinoma patients. Strengthening the monitoring and intervention of intrahepatic cholangiocarcinoma patients with poor prognosis might be critical for improving the prognosis.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is an aggressive malignancy that develops from the epithelial cells of the secondary bile duct [1]. As the second most common primary liver cancer, ICC accounts for 10–20 % of primary hepatic carcinomas and 10 % of primary hepatobiliary malignancies worldwide [2,3]. The global incidence of ICC has increased over the years [4]. Despite surgical resection, the prognosis of ICC patients remains dismal [5,6]. As a result, it is crucial to identify tumor-specific characteristics that have been associated with a short survival time and a high recurrence rate to enhance our understanding of the potential mechanism behind the development of tumors.

Lipid metabolism is considered to be related to cancer development. Several studies have demonstrated the consequences of dysregulation in lipid metabolism on the growth, progression, and metastasis of tumors [7]. High-density lipoproteins (HDLs) can encourage the removal of cholesterol from cancer cells, whereas very low-density lipoproteins (VLDLs) and low-density lipoproteins (LDLs) can supply lipids and cholesterol to cancer cells as a component for their proliferation [8]. High-density lipoprotein-associated apolipoproteins and enzymes also show anti-inflammatory and antioxidant properties [9]. Reduced levels of HDL-cholesterol (HDL-C) have been proven to have prognostic values in breast cancer (BC), lung cancer (LC), gastric cancer (GC), and colorectal cancer (CRC) [10–13]. Studies have demonstrated, in particular, that lower HDL-C levels are an independent risk factor for the development of hepatocellular carcinoma (HCC) and that preoperative blood HDL-C levels are predictive factors for hepatitis B virus-related HCC [14]. However, the prognostic role of HDL-C serum level in ICC, which also belongs to primary hepatic carcinomas, remains unknown.

In the present study, we retrospectively analyzed the clinical data of ICC patients who underwent surgery to explore the predictive role of HDL-C serum lipid level on overall survival (OS), recurrence-free survival (RFS), and early recurrence in ICC patients after surgical resection. At first, we performed a comparison analysis to assess the prognosis of patients with ICC in two groups based on their HDL-C levels: the high HDL-C group and the low HDL-C group. Subsequently, we validated the predictive significance of HDL-C levels in patients with ICC who did not have lymph node metastases. Finally, we investigated the impact of postoperative HDL-C levels on the prognosis of ICC patients with preoperative low levels of HDL-C. Our findings may act as a guide for ICC patients to control their lipid levels and encourage regular follow-ups after surgery, which will consequently reduce ICC recurrence and improve survival.

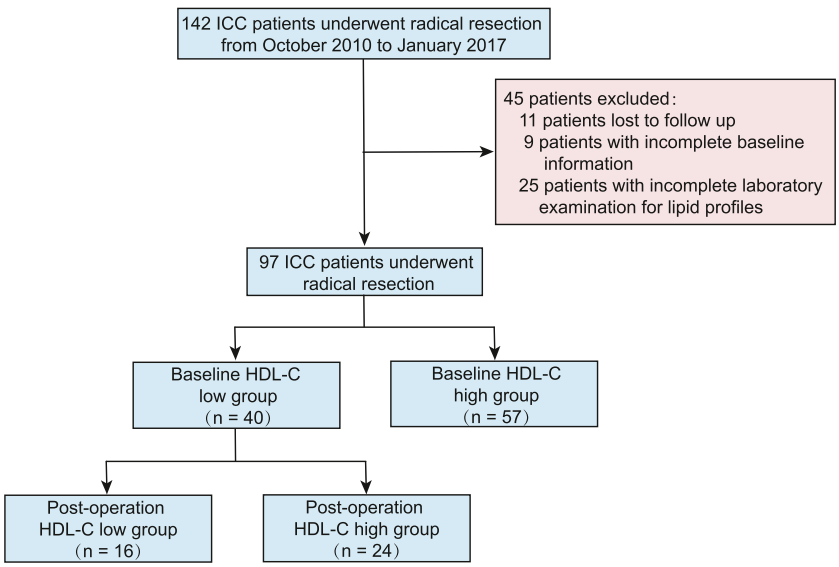

Fig. 1. The flow chart of enrollment and grouping of ICC patients.

2. Materials and methods

2.1. Patients and design

In total, 142 ICC patients who underwent surgery between October 2010 and January 2017 at the Fifth Medical Center of Chinese PLA General Hospital were enrolled. Patients were included based on the following criteria: (1) Patients with pathologically confirmed ICC; (2) those who accepted to undergo hepatic resection with regional lymph node dissection and with microscopically negative margin status; (3) patients with complete clinical medical records and follow-up data. The exclusion criteria were as follows: (1) those with incomplete laboratory examination for lipid profiles; (2) patients who received surgery, radiotherapy, chemotherapy, ablation therapy, or targeted therapy before enrollment; (3) patients with distant metastasis in preoperative evaluation. The flow chart of enrollment and grouping of patients has been shown in Fig. 1.

Finally, 97 patients with ICC were included in the analysis. The study was approved by the ethics committee of the Fifth Medical Center of Chinese PLA General Hospital (Approval number: 2019002) and complied with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Data collection

Baseline information comprising clinical characteristics, medical history, and treatments was collected from medical records. Clinical parameters were collected as follows: preoperative clinical characteristics, including age, sex, body mass index (BMI), general laboratory parameters, Eastern Cooperative Oncology Group performance status (ECOG-PST), Child-Pugh class, comorbidities, etiological factor, and medical history within 1 week before surgery; tumor characteristics, including tumor size, number, histological grade, intravascular cancer embolus, and lymph node metastasis, were recorded based on imaging report (computerized tomography [CT] and magnetic resonance imaging [MRI]) and final pathological reports. Tumor-node-metastasis (TNM) staging of tumors conformed to the 8th edition AJCC staging system.

2.3. Clinical assessment

Baseline serum lipid levels, including total cholesterol (TC), triglyceride (TG), HDL-C, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein A-I (ApoA-I), were evaluated before surgery and at subsequent follow-up visits for all patients. After fasting for at least 12 h, the lipids levels were determined using a Beckman Coulter AU 5800 chemistry analyzer (Beckman Coulter, Brea, CA).

The optimum cut-off value of HDL-C was determined by R using the "surv_cutpoint" function of the "survminer" package. The cut-off values for age and BMI are the median of total patients. Low and high cut-off values according to the standard of Fifth Medical Center of Chinese PLA General Hospital were 5.2 mmol/L for TC, 1.7 mmol/L for TG, 3.1 mmol/L for LDL-C, 1.05 g/L for ApoA-I, 40U/L for alanine aminotransferase (ALT), 40U/L for aspartate aminotransferase (AST), 50U/L for γ-glutamyl transpeptidase (GGT), 150U/L for alkaline phosphatase (ALP), 20.5umol/L for total bilirubin (TBil), and 35 g/dl for albumin (Alb). The cut-off value of tumor diameter was defined based on the 8th edition AJCC staging system.

2.4. Treatment procedures

The NCCN Clinical Practice Guidelines on ICC and the Chinese expert consensus on the management of ICC recommend selecting surgical methods based on the principles of achieving complete tumor resection with clear margins (R0) and preserving sufficient functional residual liver volume to prevent postoperative liver failure [15]. All patients involved in the study underwent surgical removal of the liver, with some patients also undergoing extra removal of the gallbladder. The status of the surgical margins was examined under a microscope and found to be negative, indicating that no cancer cells were present. Regional lymph nodes were also examined during the surgery. Types of hepatectomy were defined according to a widely accepted agreement. Major resection was defined as the resection of three or more hepatic segments, whereas minor resection was defined as the resection of two or fewer segments. Some patients received subsequent therapies after surgery, including transarterial chemoembolization (TACE), chemotherapy, alcohol ablation, and microwave ablation.

2.5. Clinical outcomes

Overall survival (OS) was defined as the time from the surgical removal of the tumor to the most recent follow-up or death. Recurrence was defined as the detection of a tumor that was confirmed by a biopsy or highly suspected to be a recurring tumor. This determination was made by an independent radiologist and hepatologist who analyzed CT/MRI images during each review. Recurrence-free survival (RFS) was calculated as the time between resection surgery and disease recurrence or death. Recurrence was divided into early and late recurrence based on a cut-off value of 2 years, early recurrence was defined as recurrence within two years after surgery.

2.6. Follow-up

The patients received surgical intervention from October 2010 to January 2017 and were last evaluated in February 2023. Every

Table 1
Clinical features of patients.

Characteristics	All patients (n = 97)
Sex	
Male	79 (81.4)
Female	18 (18.6)
Age(years)	
≤56	53 (54.6)
>56	44 (45.4)
BMI (kg/m^2)	
BMI≤23.5 kg/m^2	49 (50.5)
BMI>23.5 kg/m^2	48 (49.5)
TC (mmol/L)	
TC ≤ 5.2 mmol/L	74 (76.3)
TC > 5.2 mmol/L	23 (23.7)
TG (mmol/L)	
TG ≤ 1.7 mmol/L	76 (78.4)
TG > 1.7 mmol/L	21 (21.6)
HDL-C	
HDL-C< 0.91 mmol/L	57 (58.8)
HDL-C≥0.91 mmol/L	40 (41.2)
LDL-C (mmol/L)	
LDL-C≤3.1 mmol/L	57 (58.8)
LDL-C>3.1 mmol/L	40 (41.2)
ApoA-I (g/L)	
ApoA-1≥1.05 g/L	64 (66.0)
ApoA-1<1.05 g/L	33 (34.0)
ALT (U/L)	
ALT≤40U/L	55 (56.7)
ALT>40U/L	42 (43.3)
AST (U/L)	
AST≤40U/L	58 (59.8)
AST>40U/L	39 (40.2)
GGT (U/L)	
GGT≤50U/L	38 (39.2)
GGT>50U/L	59 (60.8)
ALP (U/L)	
ALP≤150U/L	64 (66.0)
ALP>150U/L	33 (34.0)
TBil (mmol/L)	
TBil≤20.5umol/L	67 (69.1)
TBil>20.5umol/L	30 (30.9)
Alb (g/dl)	
Alb≥35 g/dl	83 (85.6)
Alb<35 g/dl	14 (14.4)
Cirrhosis	33 (34.0)
Child-pugh grade	
A	74 (76.3)
B	23 (23.7)
Etiology factor	
Chronic HBV infection	46 (47.4)
Others	51 (52.6)
History of gallbladder disease (%)	39 (40.2)
Hepatectomy procedure (%)	
Major resection	58 (59.8)
Minor resection	39 (40.2)
Gallbladder resection (%)	51 (52.6)
AJCC stage	
AJCC stage I/II	43 (44.3)
AJCC stage III	54 (55.7)
Histological grade (%)	
Poor-differentiated	15 (15.5)
Moderate differentiated	53 (54.6)
Well-differentiated	29 (29.9)
Number of tumor lesions	
Single	69 (71.1)
Multiple	28 (28.9)
Maximum tumor diameter (cm)	
≤5 cm	40 (41.2)
>5 cm	57 (58.8)
Microvascular invasion (%)	38 (39.2)

(*continued on next page*)

Table 1 (*continued*)

Characteristics	All patients (n = 97)
Lymph node metastasis	31 (32.0)
Hypertension (%)	12 (12.4)
Diabetes (%)	3 (3.1)
Subsequent therapy (%)	28 (28.9)

AJCC: American Joint Committee on Cancer; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; ApoA-I: Apolipoprotein A-I; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: γ-glutamyl transpeptidase; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TBil: Total bilirubin; TC: Total cholesterol; TG: Triglyceride.

patient diagnosed with ICC underwent regular follow-up appointments following the clinical standards. Telephone interviews were undertaken to collect treatment information and evaluate the living conditions of patients who did not follow the suggested hospital visit.

2.7. Statistical analysis

Categorical variables were expressed as percentages and analyzed using chi-square tests. Continuous variables were presented as medians with interquartile range (IQR) and analyzed using the Mann-Whitney *U* test or *t*-test. Median follow-up time was calculated with reverse Kaplan-Meier analysis. OS and RFS were determined using the Kaplan-Meier method and compared using the likelihood ratio test. Variables from the univariate analysis with $P < 0.05$ were tested in a multivariate Cox proportional hazard model to identify independent factors associated with OS, RFS, and early recurrence. $P < 0.05$ (two-sided) was considered statistically significant. All statistical analyses were conducted using R (4.1.1).

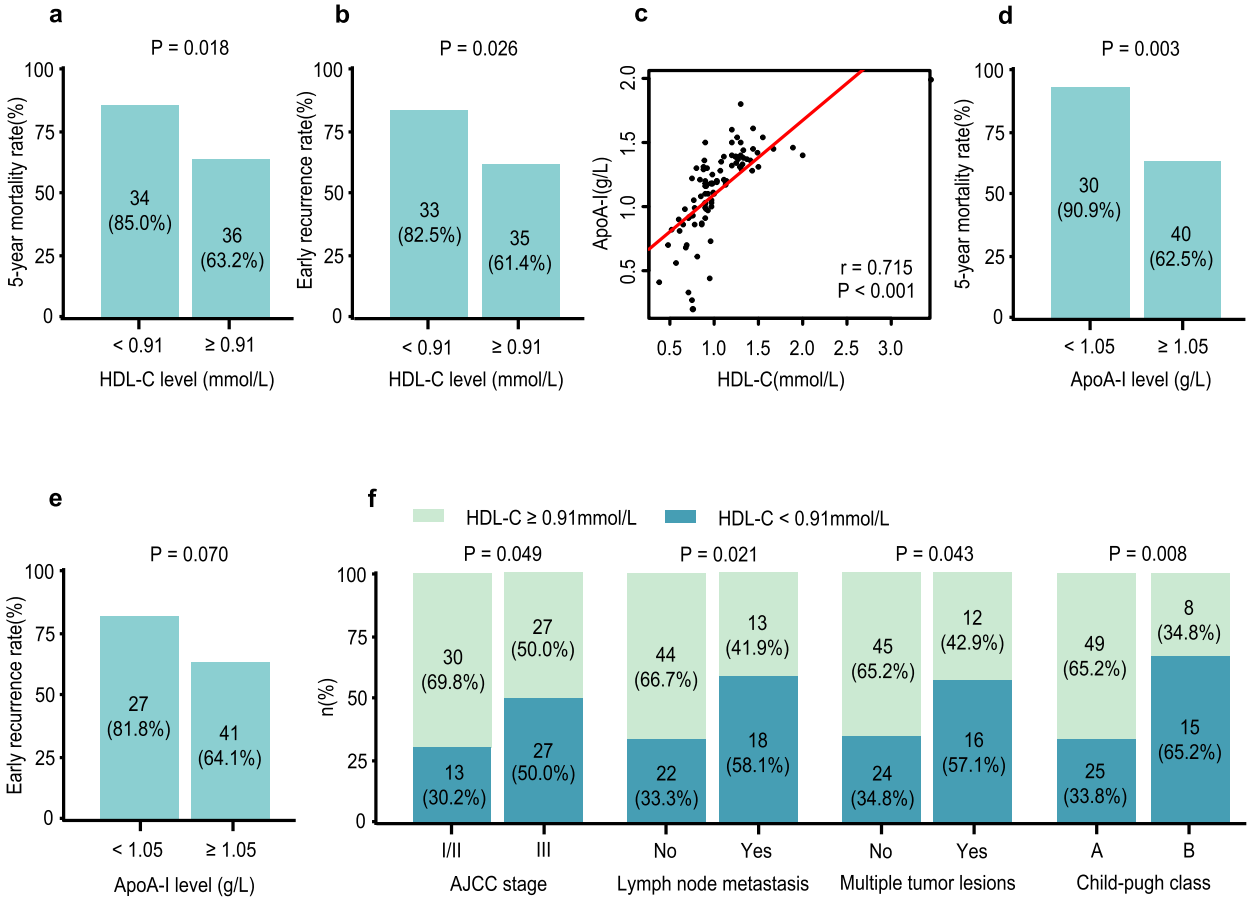

Fig. 2. Clinical outcomes of patients with ICC. (a, b) 5-year mortality rate and early recurrence rate in the high HDL-C group and low HDL-C group. (c) Correlation between serum HDL-C and ApoA-I levels. (d, e) 5-year mortality rate and early recurrence rate in the high ApoA-I group and low ApoA-I group. (f) Correlation between HDL-C level and tumor characteristics. HDL-C, high-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I.

3. Results

3.1. Baseline characteristics of patients with ICC

Between October 2010 and January 2017, a total of 97 patients with a confirmed diagnosis of ICC were enrolled. Their median age was 56 years, and 79 individuals, which accounted for 81.4 % of the total, were male. The etiology factor was chronic hepatitis B virus (HBV) infection for 46 (47.4 %) patients and a history of gallbladder disease for 39 (40.2 %) patients. Fifty-four (55.7 %) patients were diagnosed with AJCC stage III (23 patients were stage IIIA and 31 patients were stage IIIB). In total, 15 (15.5 %), 53 (54.6 %), and 29 (29.9 %) patients were categorized as poor, moderate, and well histological grade, respectively. Overall, 33 (34.0 %) patients had cirrhosis, and 74 (76.3 %) had Child-Pugh class A. Thirty-one (32.0 %) patients had lymph node metastasis, 38 (39.2 %) presented with intravascular cancer embolus, 28 (28.9 %) had more than one intrahepatic tumor lesion, and 57 (58.8 %) had a maximum tumor diameter >5 cm. 39 (40.2 %) patients underwent major liver resection while 58 (59.8 %) underwent minor resection. Additional gallbladder resections were carried out in 51 (52.6 %) patients. We divided these 97 patients based on the HDL-C cut-off value of 0.91 mmol/L into the high HDL-C group (≥0.91 mmol/L, n = 57) and the low HDL-C group (<0.91 mmol/L, n = 40) (Table 1).

3.2. Clinical outcomes of patients with ICC

The median follow-up period was 92.2 (95 % confidence interval [CI]: 79.5–116.0) months. At the end of the follow-up period, 73 (75.3 %) of 97 patients had died, and 88 (90.7 %) developed recurrence. Patients with low HDL-C levels had worse outcomes than those with high HDL-C levels. Thirty-six (63.2 %) patients from the high HDL-C group died within 5 years from surgery as compared to 34 (85.0 %) patients from the low HDL-C group (P = 0.018) (Fig. 2a). Similarly, 35 (61.4 %) patients from the high HDL-C group and 33 (82.5 %) from the low HDL-C group experienced early recurrence (P = 0.026) (Fig. 2b). After conducting Pearson's coefficient analysis, we discovered a strong linear association (r = 0.715, P < 0.001) between ApoA-I, a prominent protein in HDL-C, and HDL-C (Fig. 2c). Therefore, we divided our patient cohort into high and low ApoA-I groups based on the ApoA-I cut-off value of 1.05 g/L. The result revealed the higher 5-year mortality rate (90.9 % *vs.* 62.5 %, P = 0.003) and early recurrence rate (81.8 % *vs.* 64.1 %, P = 0.070) among the low ApoA-I patients, which corroborates our findings about HDL-C (Fig. 2d and e). In addition, we analyzed the correlation between HDL-C level and tumor characteristics and found HDL-C level to be low in higher proportion of patients diagnosed with AJCC

Table 2
Univariate analysis of the baseline clinical features to predict overall survival among patients that underwent surgical resection.

Characteristics	HR (95%CI)	P-value
HDL-C (<0.91 *vs.* ≥0.91) mmol/L	2.75(1.72–4.4)	<0.001
Lymph node metastasis (Yes *vs.* No)	2.99(1.83–4.89)	<0.001
Etiology factor (Chronic HBV infection *vs.* others)	0.44(0.27–0.7)	0.001
Multiple tumor lesions (Yes *vs.* No)	1.77(1.08–2.89)	0.022
GGT (>50 *vs.* ≤ 50) U/L	2.43(1.46–4.06)	0.001
AJCC stage (III *vs.* I or II)	2.52(1.55–4.11)	<0.001
Child-pugh grade (B *vs.* A)	2.02(1.19–3.42)	0.009
LDL-C (>3.1 *vs.* ≤3.1) mmol/L	1.81(1.13–2.88)	0.013
Major hepatectomy (Yes vs. No)	1.69(1.06–2.68)	0.028
TC (>5.2 *vs.* ≤5.2) mmol/L	1.74(1.04–2.9)	0.034
AST (>40 *vs.* ≤40) U/L	1.63(1.02–2.6)	0.04
BMI (≤23.5 *vs.* >23.5) kg/m^2	0.67(0.42–1.07)	0.096
ALT (>40 *vs.* ≤40) U/L	1.21(0.76–1.91)	0.423
ALP (>150 *vs.* ≤150) U/L	1.37(0.85–2.22)	0.194
Gallbladder resection (Yes vs. No)	1.38(0.87–2.18)	0.177
TBil (>20.5 *vs.* ≤20.5) umol/L	1.5(0.92–2.44)	0.101
Cirrhosis (Yes *vs.* No)	0.67(0.41–1.11)	0.119
Diabetes (Yes *vs.* No)	2.16(0.68–6.9)	0.194
TG (>1.7 *vs.* ≤1.7) mmol/L	1.42(0.83–2.42)	0.203
Sex (Male *vs.* Female)	0.71(0.39–1.29)	0.257
Alb (<35 *vs.* ≥35) g/dl	1.2(0.64–2.23)	0.573
Hypertension (Yes *vs.* No)	1.26(0.63–2.54)	0.514
Subsequent therapy (Yes *vs.* No)	1.17(0.71–1.94)	0.532
Maximum tumor diameter (>5 *vs.* ≤5) cm	1.15(0.72–1.84)	0.569
Age (≤56 *vs.* >56) years	0.94(0.59–1.49)	0.784
Differentiation	0.96(0.68–1.34)	0.795
Moderate *vs.* Well	1.20(0.71–2.04)	0.491
Poor *vs.* Well	1.03(0.50–2.16)	0.93
Microvascular invasion (Yes *vs.* No)	1.18(0.74–1.88)	0.488
History of gallbladder disease (Yes *vs.* No)	1.04(0.65–1.66)	0.875

AJCC: American Joint Committee on Cancer; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: γ-glutamyl transpeptidase; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TBil: Total bilirubin; TC: Total cholesterol; TG: Triglyceride.

stage III (50.0 % *vs.* 30.2 %, P = 0.049), lymph node metastasis (58.1 % *vs.* 33.3 %, P = 0.021), multiple tumor lesions (57.1 % *vs.* 34.8 %, P = 0.043), or Child-Pugh class B (65.2 % *vs.* 33.8 %, P = 0.008) (Fig. 2f).

3.3. HDL-C level was associated with OS and RFS of ICC patients

As shown in Table 2, univariate analysis results demonstrated several factors such as HDL-C level, lymph node metastasis, AJCC stage, etiology factor, multiple tumor lesions, GGT, Child-Pugh class, LDL-C, hepatectomy procedure, TC, and AST that were related to OS among ICC patients that had undergone surgical resection (all P < 0.05). We included all of these factors in the multivariate analysis that showed HDL-C level (<0.91 *vs.* ≥ 0.91 mmol/L, hazard ratio [HR] = 2.55; 95 % CI: 1.38–4.71; P = 0.003), lymph node metastasis (Yes *vs.* No, HR = 2.58; 95 % CI: 1.28–5.19; P = 0.008), etiology factor (chronic HBV infection *vs.* others, HR = 0.5; 95 % CI: 0.28–0.88; P = 0.016) and multiple tumor lesions (Yes *vs.* No, HR = 1.85; 95 % CI: 1.01–3.39; P = 0.047) as the independent factors associated with the OS of ICC patients (Table 3).

Patients with low HDL-C levels had a median OS of 10.0 months (95 % CI: 7.9–15.9), which was significantly lower than the median OS of 35.7 months (95 % CI: 28.0–52.8) observed for the patients with high HDL-C levels (P < 0.001) (Fig. 3a).

When investigating RFS, the results of the univariate analysis showed that HDL-C, AJCC stage, etiology factor, lymph node metastasis, GGT, multiple tumor lesions, and BMI were all associated with ICC patients' RFS following surgery (all P < 0.05) (Table 4). Multivariate analysis conducted including all the above factors confirmed HDL-C level as an independent factor related to PFS (<0.91 *vs.* ≥ 0.91 mmol/L, HR = 1.86; 95 % CI: 1.19–2.92; P = 0.007) (Table 5).

In particular, the median RFS for the patients with high HDL-C levels was 15.2 months (95 % CI: 10.2–26.4), which was significantly longer than that of 5.4 months (95 % CI: 4.4–9.1) reported for those with low HDL-C levels (Fig. 3b).

Due to its colinear connection with HDL-C, we excluded the ApoA-I level from both univariate and multivariate Cox regression analysis. Nevertheless, our analysis revealed that patients in the high ApoA-I group exhibited substantially better median OS (33.3 vs. 12.7 months, P < 0.001) and RFS (11.8 vs. 6.4 months, P = 0.003) compared to those in the low ApoA-I group. These findings further support the association between HDL-C and patient outcomes (Fig. 3c and d).

3.4. HDL-C level was associated with early recurrence of ICC patients

We conducted additional univariate and multivariate analyses to investigate factors associated with early recurrence in ICC patients who underwent surgical resection. As shown in Table 6, HDL-C level, AJCC stage, etiology factor, multiple tumor lesions, and lymph node metastasis were related to early recurrence among ICC patients after surgery (all P < 0.05). Further multivariate analysis demonstrated HDL-C level (<0.91 *vs.* ≥ 0.91 mmol/L, HR = 2.07; 95 % CI: 1.26–3.41; P = 0.004), etiology factor (chronic HBV infection *vs.* others, HR = 0.49; 95 % CI: 0.29–0.84; P = 0.01), and multiple tumor lesions (Yes *vs.* No, HR = 2.00; 95 % CI: 1.14–3.51; P = 0.016) as the factors independently associated with early recurrence in ICC patients (Table 7). Therefore, it can be hypothesized that individuals with low levels of HDL-C were more susceptible to early recurrence. Furthermore, patients who had many tumor lesions or did not have HBV infection had a higher likelihood of experiencing early recurrence.

3.5. HDL-C level was associated with the prognosis of ICC patients without lymph node metastasis

We also validated the role of HDL-C in the prognosis of ICC patients without lymph node metastasis. Patients without lymph node metastasis had better OS (30.9 *vs.* 11.3 months, P < 0.001) and RFS (11.7 *vs.* 6.8 months, P = 0.008) than those with lymph node metastasis (Fig. 4a and b).

Multivariate analysis results (Table 8) revealed the independent association of HDL-C level (<0.91 *vs.* ≥ 0.91 mmol/L) with OS (HR = 2.20; 95 % CI: 1.09–4.46; P = 0.028), RFS (HR = 1.83; 95 % CI: 1.04–3.21; P = 0.036), and early recurrence (HR = 2.22; 95 % CI: 1.19–4.13; P = 0.012) in patients without lymph node metastasis. Patients with low HDL-C levels had a significantly lower median OS

Table 3
Multivariable Cox regression analysis of the baseline clinical features to predict overall survival among patients that underwent surgical resection.

Characteristics	HR (95%CI)	P-value
HDL-C (<0.91 *vs.* ≥0.91) mmol/L	2.55(1.38–4.71)	0.003
Lymph node metastasis (Yes *vs.* No)	2.58(1.28–5.19)	0.008
Etiology factor (Chronic HBV infection *vs.* others)	0.5(0.28–0.88)	0.016
Multiple tumor lesions (Yes *vs.* No)	1.85(1.01–3.39)	0.047
GGT (>50 *vs.* ≤ 50) U/L	1.84(1–3.41)	0.051
AJCC stage (III *vs.* I or II)	1.02(0.52–1.98)	0.963
Child-pugh grade (B *vs.* A)	0.57(0.26–1.25)	0.161
LDL-C (>3.1 *vs.* ≤3.1) mmol/L	1.05(0.56–1.98)	0.868
Major hepatectomy (Yes vs. No)	0.99(0.55–1.78)	0.975
TC (>5.2 *vs.* ≤5.2) mmol/L	1.19(0.58–2.46)	0.63
AST (>40 *vs.* ≤40) U/L	1.24(0.62–2.49)	0.551

AJCC: American Joint Committee on Cancer; AST: Aspartate aminotransferase; GGT: γ-glutamyl transpeptidase; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride.

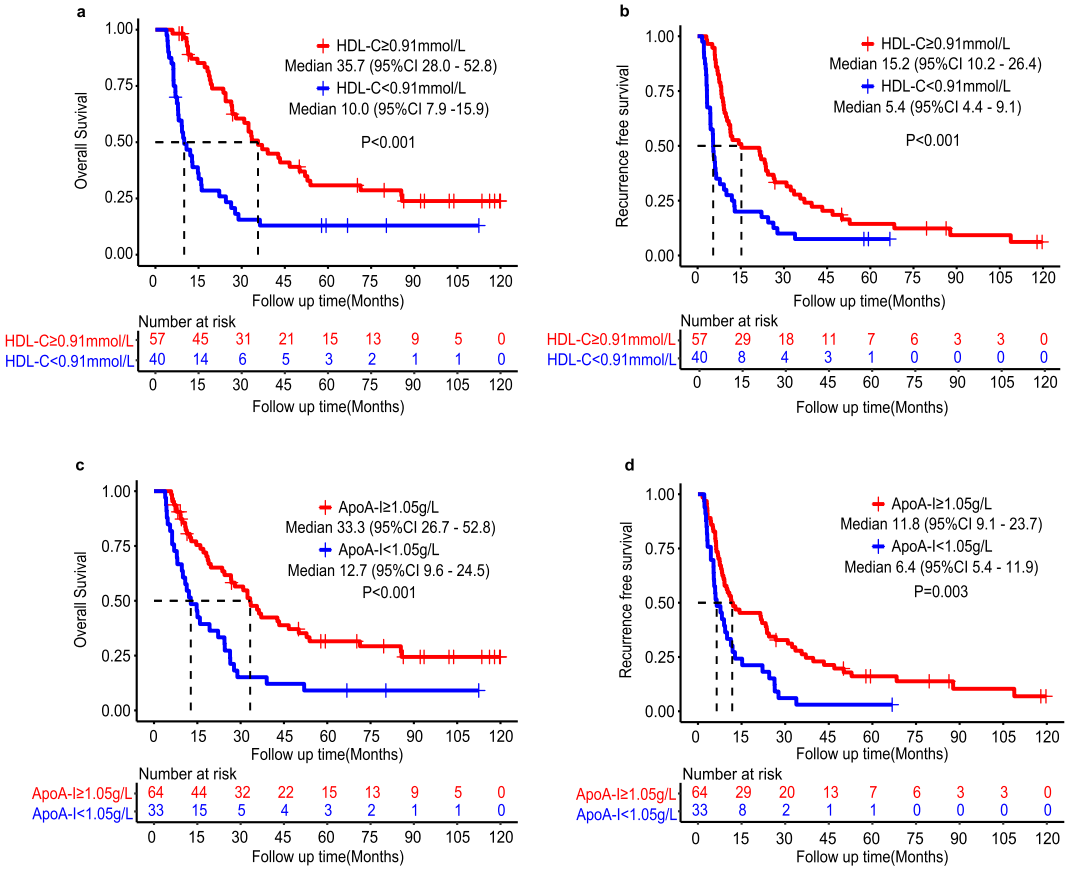

Fig. 3. Survival outcomes of patients with ICC. (a, b) Survival outcomes in the high HDL-C group and low HDL-C group. (a) Overall survival. (b) Recurrence-free survival. (c, d) Survival outcomes in the high ApoA-I group and low ApoA-I group. (c) Overall survival. (d) Recurrence-free survival. HDL-C, high-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I.

of 14.8 months (95 % CI: 9.1-NA) than those with high HDL-C levels (43.3 months, 95 % CI: 28.0–85.5) (P = 0.031) (Fig. 4c). The median RFS was 5.7 months (95 % CI: 4.5–12.9) for the HDL-C low group, which was significantly lower than that of 21.8 months (95 % CI: 11.4–30.9) observed for the HDL-C high group (P = 0.042) (Fig. 4d).

3.6. Clinical outcomes of ICC patients with low pre-operation HDL-C levels

To assess the impact of post-operative HDL-C levels on the prognosis of ICC patients, we categorized patients with low pre-operative HDL-C levels into two groups: a low post-operative HDL-C group and a high post-operative HDL-C group, based on their HDL-C levels three months following surgery. Our results showed that patients with low post-operation HDL-C levels had a median OS of 6.6 months (95 % CI: 4.7–15.0), which was markedly shorter than the median OS of 15.3 months (95 % CI: 10.8–28.9) in patients with high post-operation HDL-C levels (P < 0.001) (Fig. 5a). Additionally, the median RFS for the patients with low post-operation HDL-C levels was 3.8 months (95 % CI: 2.9–6.0), which was significantly lower than that of 7.1 months (95 % CI: 5.6–24.5) reported for those with low HDL-C levels (Fig. 5b).

4. Discussion

In this study, we retrospectively investigated the correlation between HDL-C levels and prognosis in 97 ICC patients who underwent surgery. Our findings strongly hint at the potential role of HDL-C level as a prognosis indicator in ICC patients who have undergone surgical resection. Furthermore, perioperative control of HDL-C may help improve ICC patient outcomes.

Recent research has shown an increasing amount of evidence indicating a possible link between levels of HDL-C and the occurrence and advancement of different types of cancers. Lucilla et al. reported that low HDL-C levels predict HCC development in individuals with liver fibrosis, and highlighted the importance of integrating clinical approaches with dietary regimens and a healthy lifestyle to prevent HCC [16]. It has also been found that increased pre-operative plasma HDL-C levels were associated with increased DFS and OS after HCC radical surgery [14]. A retrospective study conducted by Bo et al. showed that preoperative serum HDL-C level was closely associated with distant metastasis of patients with gallbladder cancer (GBC), and HDL-C level may be a valuable prognostic factor for

Table 4
Univariate analysis of baseline clinical features for prediction of recurrence free-survival among patients that underwent surgical resection.

Characteristics	HR (95%CI)	P-value
HDL-C (<0.91 *vs.* ≥0.91) mmol/L	2.2(1.43–3.4)	<0.001
AJCC stage (III *vs.* I or II)	2.23(1.43–3.48)	<0.001
Etiology factor (Chronic HBV infection *vs.* others)	0.54(0.35–0.82)	0.004
Lymph node metastasis (Yes *vs.* No)	1.87(1.2–2.92)	0.008
GGT (>50 *vs.* ≤ 50) U/L	1.72(1.09–2.69)	0.019
Multiple tumor lesions (Yes *vs.* No)	1.66(1.05–2.62)	0.03
BMI (≤23.5 *vs.* >23.5) kg/m^2	0.63(0.41–0.97)	0.036
TBil (>20.5 *vs.* ≤20.5) umol/L	1.38(0.88–2.18)	0.163
Subsequent therapy (Yes *vs.* No)	1.36(0.86–2.16)	0.189
Cirrhosis (Yes *vs.* No)	0.74(0.47–1.15)	0.181
TC (>5.2 *vs.* ≤5.2) mmol/L	1.31(0.81–2.12)	0.265
Sex (Male *vs.* Female)	0.73(0.42–1.28)	0.275
Maximum tumor diameter (>5 *vs.* ≤5) cm	1.13(0.74–1.73)	0.579
LDL-C (>3.1 *vs.* ≤3.1) mmol/L	1.26(0.83–1.93)	0.28
AST (>40 *vs.* ≤40) U/L	1.28(0.83–1.96)	0.257
ALP (>150 *vs.* ≤150) U/L	1.26(0.81–1.96)	0.31
ALT (>40 *vs.* ≤40) U/L	0.95(0.62–1.45)	0.816
TG (>1.7 *vs.* ≤1.7) mmol/L	1.02(0.61–1.69)	0.945
Diabetes (Yes *vs.* No)	1.25(0.39–3.96)	0.708
Child-pugh grade (B *vs.* A)	1.57(0.96–2.58)	0.072
Gallbladder resection (Yes *vs.* No)	1.15(0.76–1.75)	0.516
Major hepatectomy (Yes *vs.* No)	1.23(0.8–1.88)	0.343
Alb (<35 *vs.* ≥35) g/dl	0.93(0.5–1.72)	0.818
Microvascular invasion (Yes *vs.* No)	0.98(0.63–1.51)	0.922
Hypertension (Yes *vs.* No)	0.92(0.47–1.78)	0.797
Age (≤56 *vs.* >56) years	1.1(0.72–1.68)	0.65
Differentiation	1(0.75–1.35)	0.985
Moderate *vs.* Well	1.39(0.86–2.25)	0.177
Poor *vs.* Well	0.87(0.45–1.71)	0.697
History of gallbladder disease (Yes *vs.* No)	1.06(0.7–1.62)	0.779

AJCC: American Joint Committee on Cancer; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: γ-glutamyl transpeptidase; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TBil: Total bilirubin; TC: Total cholesterol; TG: Triglyceride.

Table 5
Multivariable Cox regression analysis of baseline clinical features for prediction of recurrence free-survival among patients that underwent surgical resection.

Characteristics	HR (95%CI)	P-value
HDL-C (<0.91 *vs.* ≥0.91) mmol/L	1.86(1.19–2.92)	0.007
AJCC stage (III *vs.* I or II)	1.68(0.93–3.03)	0.083
Etiology factor (Chronic HBV infection *vs.* others)	0.64(0.38–1.07)	0.088
Lymph node metastasis (Yes *vs.* No)	1.07(0.59–1.92)	0.83
GGT (>50 *vs.* ≤ 50) U/L	1.37(0.84–2.22)	0.203
Multiple tumor lesions (Yes *vs.* No)	1.62(0.98–2.68)	0.059
BMI (≤23.5 *vs.* >23.5) kg/m^2	0.92(0.57–1.51)	0.75

AJCC: American Joint Committee on Cancer; BMI: Body Mass Index; GGT: γ-glutamyl transpeptidase; HDL-C: High-Density Lipoprotein Cholesterol.

GBC patients [17]. Prior research has also uncovered abnormal lipid metabolism in individuals diagnosed with cholangiocarcinoma. For instance, the study revealed that individuals with cholangiocarcinoma had elevated levels of TG and decreased levels of HDL compared to patients with cholelithiasis and the control group [18]. In this study, we investigated for the first time the relationship between HDL-C levels and prognosis in ICC patients. Interestingly, our findings also showed consistent results with other types of cancers in previous studies: following a median follow-up period of 92.2 months, it was established that a low serum level of HDL-C is an independent risk factor associated with poorer OS and RFS in patients with ICC who had undergone surgery. To ensure the robustness of our findings, we limited the research to patients who did not have lymph node metastases. We discovered that the level of HDL-C continues to be a valuable predictor for predicting survival and recurrence, even among individuals who typically have more favorable clinical outcomes.

Published findings indicate that a significant factor leading to the unfavorable outlook for patients with ICC following surgical removal is the high rate of recurrence, with early recurrence being more prevalent than late recurrence [19]. Certain inherent traits or properties of the tumor can contribute to a higher likelihood of early recurrence after treatment [20]. In addition, patients who have early recurrence generally have poorer long-term prognoses compared to those who experience late recurrence [21,22]. Hence, it is

Table 6
Univariate analysis of baseline clinical features for early recurrence prediction among patients that underwent surgical resection.

Characteristics	HR (95%CI)	P-value
HDL-C (<0.91 *vs.* ≥0.91) mmol/L	2.52(1.56–4.08)	<0.001
Etiology factor (Chronic HBV infection *vs.* others)	0.49(0.3–0.79)	0.004
Multiple tumor lesions (Yes *vs.* No)	1.85(1.11–3.07)	0.019
AJCC stage (III *vs.* I or II)	2.13(1.29–3.52)	0.003
Lymph node metastasis (Yes *vs.* No)	1.67(1.02–2.75)	0.042
GGT (>50 *vs.* ≤ 50) U/L	1.57(0.95–2.59)	0.081
Child-pugh grade (B *vs.* A)	1.38(0.8–2.36)	0.248
Cirrhosis (Yes *vs.* No)	0.74(0.44–1.23)	0.244
AST (>40 *vs.* ≤40) U/L	1.31(0.81–2.13)	0.267
BMI (≤23.5 *vs.* >23.5) kg/m^2	0.77(0.48–1.24)	0.281
Subsequent therapy (Yes *vs.* No)	1.54(0.93–2.56)	0.092
Diabetes (Yes *vs.* No)	1.14(0.28–4.67)	0.853
Differentiation		
Moderate *vs.* Well	1.63(0.94–2.82)	0.081
Poor *vs.* Well	0.9(0.41–1.99)	0.794
Age (≤56 *vs.* >56) years	1.04(0.64–1.67)	0.882
Alb (<35 *vs.* ≥35) g/dl	0.84(0.42–1.7)	0.633
Gallbladder resection (Yes *vs.* No)	1.11(0.69–1.79)	0.657
Major hepatectomy (Yes *vs.* No)	1.14(0.7–1.85)	0.605
Sex (Male *vs.* Female)	0.62(0.32–1.22)	0.168
TBil (>20.5 *vs.* ≤20.5) umol/L	1.22(0.74–2.03)	0.438
TC (>5.2 *vs.* ≤5.2) mmol/L	1.11(0.64–1.92)	0.718
TG (>1.7 *vs.* ≤1.7) mmol/L	0.87(0.47–1.59)	0.651
Microvascular invasion (Yes *vs.* No)	0.95(0.58–1.56)	0.838
ALP (>150 *vs.* ≤150) U/L	1.1(0.67–1.8)	0.721
Maximum tumor diameter (>5 *vs.* ≤5) cm	1.07(0.66–1.74)	0.78
ALT (>40 *vs.* ≤40) U/L	0.97(0.6–1.57)	0.905
History of gallbladder disease (Yes *vs.* No)	0.8(0.49–1.31)	0.376
Hypertension (Yes *vs.* No)	1.15(0.57–2.32)	0.701
LDL-C (>3.1 *vs.* ≤3.1) mmol/L	1.19(0.74–1.93)	0.47

AJCC: American Joint Committee on Cancer; Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; GGT: γ-glutamyl transpeptidase; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TBil: Total bilirubin; TC: Total cholesterol; TG: Triglyceride.

Table 7
Multivariable Cox regression analysis of baseline clinical features for early recurrence prediction among patients that underwent surgical resection.

Characteristics	HR (95%CI)	P-value
HDL-C (<0.91 *vs.* ≥0.91) mmol/L	2.07(1.26–3.41)	0.004
Etiology factor (Chronic HBV infection *vs.* others)	0.49(0.29–0.84)	0.01
Multiple tumor lesions (Yes *vs.* No)	2(1.14–3.51)	0.016
AJCC stage (III *vs.* I or II)	1.58(0.84–2.96)	0.157
Lymph node metastasis (Yes *vs.* No)	0.89(0.48–1.66)	0.722

AJCC: American Joint Committee on Cancer; HDL-C: High-Density Lipoprotein Cholesterol.

crucial to ascertain the parameters linked to early recurrence following surgery. Our research found that baseline HDL-C levels were significantly associated with ICC tumor characteristics including AJCC stage, lymph node metastasis, number of tumor lesions and Child-Pugh class, additionally, low HDL-C level was associated with early recurrence after ICC surgery. Gaya et al. discovered that performing a secondary hepatectomy after recurrence resulted in improvement in survival for individuals with ICC [23]. In addition, system chemotherapy, TACE, and ablation could also be considered as the treatment of choice for ICC recurrence. Therefore, even if the prognosis of patients with early recurrence of ICC after primary hepatectomy is poor, appropriate treatment should be considered to improve the prognosis. Consequently, for ICC patients with low HDL-C levels, implementing a rigorous surveillance program will ensure that patients receive necessary medical treatment promptly at the early stage of recurrence.

We collected patients' serum lipid levels at follow-up and separated patients with low pre-operation HDL-C levels into two groups based on the HDL-C levels at three months following surgery to assess the impact of post-operation HDL-C levels on the clinical outcomes of ICC. Compared to the OS and PFS of these two groups, our results suggest that ICC patients who had consistently low HDL-C levels exhibited a less favorable prognosis. The findings indicate that the HDL-C levels after surgery might also associated with the prognosis of ICC patients. Furthermore, controlling HDL-C levels following surgery may help patients with low pre-operative levels of cholesterol. It is important to note that we did not distinguish between patients receiving lipid-lowering drugs (LLDs) and those with elevated HDL-C levels following surgery because of the small number of patients in this investigation. Therefore, it is necessary to

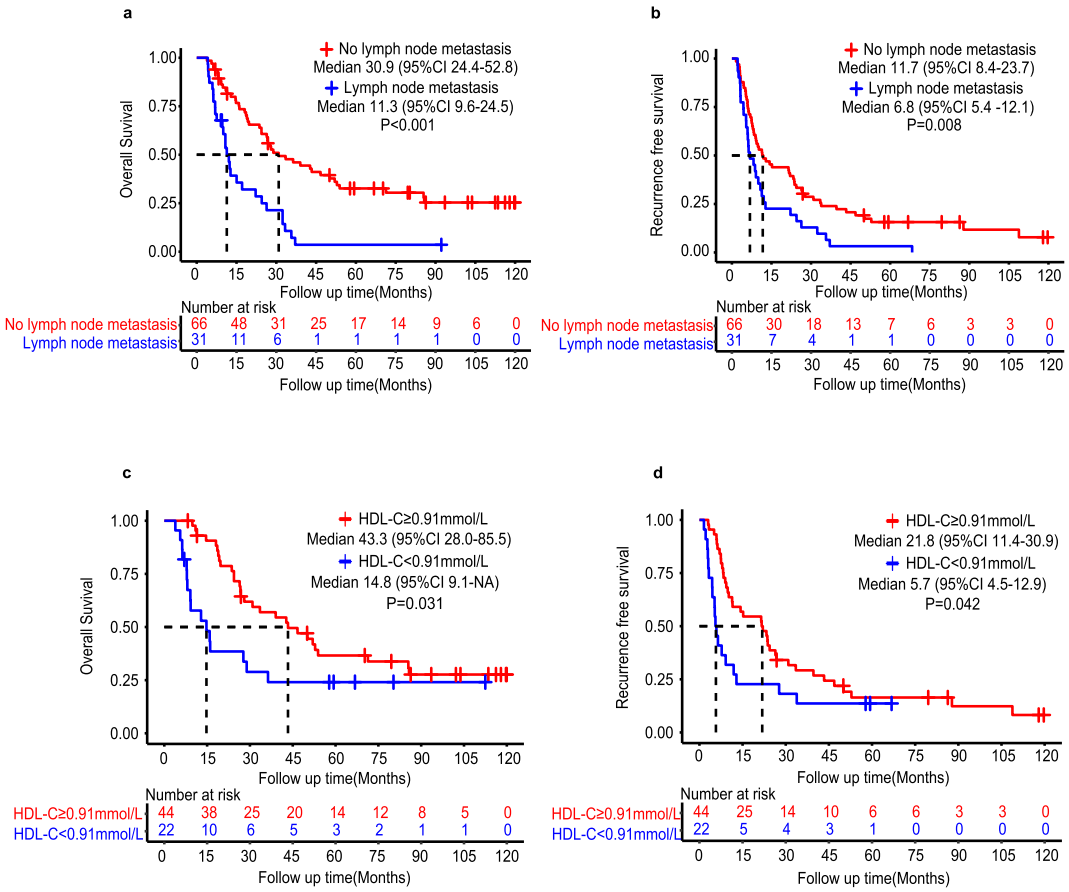

Fig. 4. Survival outcomes in patients without lymph node metastasis. (a, b) Survival outcomes in patients with and without lymph node metastasis. (a) Overall survival. (b) Recurrence-free survival. (c, d) Survival outcomes in patients without lymph node metastasis from the high HDL-C and low HDL-C groups. (c) Overall survival. (d) Recurrence-free survival. HDL-C, high-density lipoprotein cholesterol.

Table 8
Multivariable Cox regression analysis of baseline clinical features for overall survival, recurrence-free survival, and early recurrence among patients without lymph node metastasis that underwent surgical resection.

Characteristics	Overall survival		Recurrence-free survival		Early recurrence	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
HDL-C (<0.91 *vs.* ≥0.91) mmol/L	2.2 (1.09–4.46)	0.028	1.83 (1.04–3.21)	0.036	2.22 (1.19–4.13)	0.012

[a]Multivariable Cox regression analysis of overall survival adjusted for HDL-C, LDL-C, Etiology factor, GGT, TC, and Child-pugh grade. Multivariable Cox regression analysis of recurrence-free survival adjusted for HDL-C, AJCC stage, Etiology factor, and BMI. Multivariable Cox regression analysis of early recurrence adjusted for HDL-C, AJCC stage, and Etiology factor.
[b]AJCC: American Joint Committee on Cancer; BMI: Body mass index; GGT: γ-glutamyl transpeptidase; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol.

conduct further large-scale research to confirm whether the utilization of LLDs can indeed help improve the prognosis of ICC patients with abnormal HDL-C levels.

While the precise underlying process is still unclear, evidence from published studies may provide some explanation as to why individuals with aberrant HDL-C levels experience worse clinical outcomes. Abnormal changes in lipid metabolism can have a negative impact on the tumor microenvironment. HDL-C has been empirically documented to possess antioxidant and anti-inflammatory properties in relation to cancer. Conversely, the absorption of cholesterol by tumor cells may potentially lead to a reduction in blood HDL-C levels, hence promoting tumor growth [24,25]. ApoA-I, on the other hand, is a major protein component of HDL-C that is active in the tumor microenvironment and participates in tumor growth, immune cells, and tumor proliferation [26]. Ma et al. found that ApoA-I could downregulate the mitogen-activated protein kinase (MAPK) signaling pathway to promote cell apoptosis and inhibit the proliferation of HCC cells [27]. Peng et al. also reported that ApoA-I mimetic peptide L-4F could exert anti-tumor and immunomodulatory effects by inhibiting granulocytic myeloid-derived suppressor cells (PMN-MDSCs) in pancreatic cancer by regulating

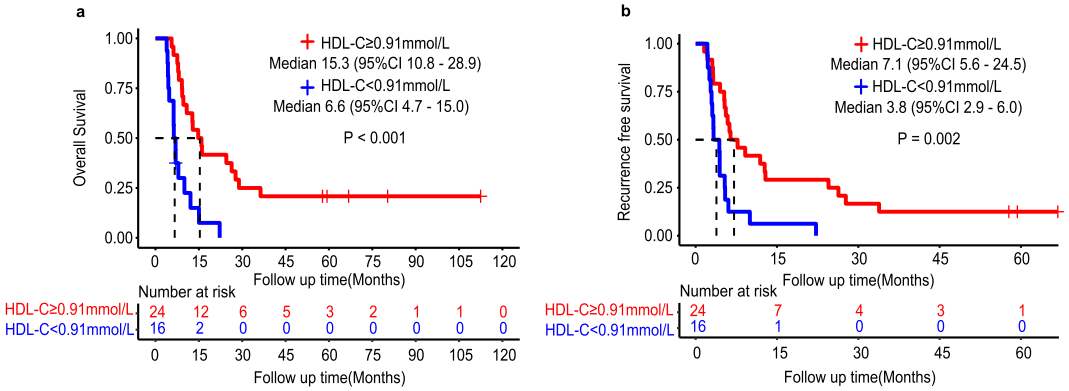

Fig. 5. Survival outcomes in patients with pre-operation low HDL-C levels. (a, b) Survival outcomes in the post-operation high HDL-C group and post-operation low HDL-C group. (a) Overall survival. (b) Recurrence-free survival. HDL-C, high-density lipoprotein cholesterol.

signal transducer and activator of transcription 3 (STAT3) signaling pathway [28]. However, the potential molecular mechanism of HDL-C associated with tumor development still needs to be further explored.

Consistent with the 8th edition of the AJCC staging manual, our investigation found comparable prognostic markers, such as lymph node metastases and numerous tumor lesions. Moreover, we establish that the etiology factor and GGT levels were important predictors of clinical outcomes in ICC. Previous studies have shown that individuals with HBV infection had considerably superior clinical outcomes in terms of OS, RFS, and early recurrence compared to those without HBV infection, as observed in the univariate analysis [29]. GGT is a known marker of tumor progression and survival in various cancers, and its importance in survival prediction among ICC patients has been previously described [30]. We also found that the GGT level was significantly associated with OS and RFS in ICC.

The repeated-measure approach and active 7-year follow-up of ICC patients are two of this study's strengths. Low HDL-C levels are a useful laboratory diagnostic that can be utilized as a warning sign to identify high-risk patients and potentially improve their care. Moreover, our results imply that perioperative HDL-C management may enhance prognosis in appropriately selected individuals.

Our study has several limitations. First, given its retrospective nature and the small number of patients involved, the possibility of residual confounding factors cannot be excluded. Second, due to the limited number of patients included in this study, we did not differentiate whether patients with elevated levels of HDL-C after surgery were using any LLDs. Third, we did not investigate the association between recurrence treatment mode and long-term outcomes among relapsed patients since there were not many patients who received postoperative adjuvant therapy for relapse, particularly adjuvant chemotherapy. Subsequent large-scale, multi-center clinical prospective trials ought to confirm the preliminary results presented here and ascertain the specific mechanisms underlying lipid metabolism in ICC.

5. Conclusions

In conclusion, this long-term follow-up study of ICC patients who underwent surgical resection confirmed that HDL-C level is an independent factor for OS, RFS, and early recurrence. Our findings highlight the importance of monitoring and controlling HDL-C levels in ICC patients, as low HDL-C levels may reflect poor prognosis. This finding will guide ICC patients with low HDL-C levels to use LLDs rationally and undergo regular follow-ups for early treatment of recurrent lesions and improved clinical outcomes.

Ethical approval

This study was approved by the ethics committee of the Fifth Medical Center of Chinese PLA General Hospital, approval number [2019002]. Based on the retrospective nature of the study, the need for written informed consent was waived by the Ethics Review Committee of Chinese PLA General Hospital. The study was performed by the ethics standards of the institutional research committee and the recent Declaration of Helsinki.

Financial support

This study was funded by the State Key Projects Specialized on Infectious Disease, Chinese Ministry of Science and Technology, China (2018ZX10302205-001), National Health Commission Medical and Health Science and Technology Development Research Center, China (WKZX2023CX020011), Natural Science Foundation of Beijing Municipality, China (7212099) and National Natural Science Foundation of China, China (81902495).

Potential competing interests

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject

of this article.

Data availability statement

All data in the present study are available from the authors.

CRediT authorship contribution statement

Shu-Min Yu: Writing – original draft, Project administration, Formal analysis. **Xiu-Juan Chang:** Writing – original draft, Formal analysis. **Yue-Yue Gu:** Formal analysis, Data curation. **Xiao-Dong Jia:** Methodology, Funding acquisition. **Xu-Dong Gao:** Writing – review & editing, Methodology. **Jia-Gan Huang:** Validation, Resources. **Jing-Hui Dong:** Resources, Project administration. **Zhen Zeng:** Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing 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 paper.

Abbreviations

Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ApoA-I:	Apolipoprotein A-I;
AST	aspartate aminotransferase
HDL-C:	High-Density Lipoprotein Cholesterol
HR	Hazard ratios
ICC	Intrahepatic cholangiocarcinoma
GGT	γ-glutamyl transpeptidase
LDL-C:	Low-Density Lipoprotein Cholesterol
LLDs	lipid-lowering drugs; OS: Overall survival
RFS	Recurrence-free survival
TBil	total bilirubin
TC	Total cholesterol
TG	Triglyceride;
95 % CI	95 % confidence interval

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