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SYSTEMATIC REVIEW

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Prognostic value of albumin-bilirubin grade in patients with cholangiocarcinoma: a systematic review and meta-analysis

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Abstract

Background Cholangiocarcinoma (CCA) is a type of cancer that develops in the biliary tract. CCA accounts for 10% of primary hepatic cancers and is characterized by its aggressive nature and poor prognosis. This systematic review and meta-analysis aims to assess the prognostic value of the novel hepatic function assessment measure known as albumin-bilirubin (ALBI) grade in patients with CCA.

Method A comprehensive search was conducted on PubMed, Web of Science, Embase, and Scopus databases until August 11, 2023. Studies examining the prognostic impact of ALBI grade in patients with CCA were included. The prognostic effect was evaluated using hazard ratio (HR) with 95% confidence intervals (CI). The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS). The final meta-analysis was performed using R version 4.3.1.

Results The final meta-analysis included 13 studies with 3,434 patients. In univariate analysis (HR = 1.90, 95% CI: 1.65–2.19, $P < 0.01$) and multivariate analysis (HR = 1.88, 95% CI: 1.41–2.52, $P < 0.01$), higher ALBI grade was associated with lower overall survival (OS) in patients with intrahepatic CCA (ICCA). Higher ALBI grade was also correlated with decreased recurrence-free survival (RFS), with an HR of 1.63 (95% CI: 1.36–1.97, $P < 0.01$). Subgroup analysis of different ALBI grade comparisons showed consistent findings with our pooled data.

Conclusion A high ALBI grade indicates poor OS and RFS in patients with CCA especially intrahepatic type. ALBI should be considered a reliable and clinically useful prognostic indicator.

Registration PROSPERO ID: CRD42022379877

Keywords Albumin-bilirubin grade, ALBI grade, Cholangiocarcinoma, Intrahepatic cholangiocarcinoma, Prognosis, Prognostic factor, Overall survival, Disease-free survival

Introduction

Cholangiocarcinoma (CCA) is a diverse group of cancers that can occur at any location within the biliary tract system, arising from the lining epithelium of the biliary tract (cholangiocytes) and peribiliary glands. Based on anatomical involvement, it is classified into intrahepatic CCA (ICCA), peri-hilar CCA, and distal CCA [1]. CCA is the second most common primary liver malignancy after hepatocellular carcinoma,

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representing around 10%-15% of primary hepatobiliary malignancies and less than 3% of gastrointestinal malignant tumors. The prognosis for CCA is generally poor, with a 5-year survival rate less than 10% [2]. Surgical resection is the only curative option for patients with CCA. However, only 30–60% of tumors are resectable. Survival outcomes in surgically treated patients are still disappointing. The prognosis of CCA in both surgical and non-surgical treatments is not satisfactory. Therefore, unique prognostic tools are needed to be established to guide clinicians in choosing the best treatment option for patients [3, 4].

Multiple studies suggested variable prognostic tools associated with poor survival outcomes in patients with CCA, including multiple lesions, large tumors, advanced tumor stage, lymph node involvement, treatment method (surgical vs. non-surgical), and an elevated level of CA19-9 [5–7]. These varying findings emphasize the importance of considering multiple clinical and pathological factors to improve prognostic predictions and guide treatment decisions for these complex malignancies. Therefore, a comprehensive and individualized approach is crucial when assessing and managing different types of CCA.

A novel prognostic indicator for liver function, known as the albumin-bilirubin (ALBI) grade, was initially introduced by Johnson et al. in 2015 based on the patient's serum albumin and bilirubin levels to evaluate liver function in patients with hepatocellular carcinoma (HCC). Low albumin level with increased bilirubin level results in a high ALBI grade [8]. Albumin level indicates patient's nutritional status and body's ability to cope with inflammation. Additionally, a higher bilirubin level suppresses antitumor response by lymphocytes, leading to tumor progression and negatively affect patient's survival outcome [9]. Therefore, it is expected that higher ALBI grade indicates poor survival. Calculation of ALBI grade is way easier than other prognostic factor like TNM stage and histological grade and only requires a simple blood test. ALBI grade is also not affected by subjective assessment like ascites and hepatic encephalopathy seen in Child–Pugh [10]. ALBI grade has been proposed as a reliable prognostic indicator for individuals with liver disorders such as HCC, hepatitis-B-related cirrhosis, primary biliary cirrhosis, acute-on-chronic liver failure [11]. In the case of patients with CCA, the predictive utility of ALBI grade can be explained through various mechanisms. Firstly, the ALBI grade reflects the functional reserve of the liver, which can impact a patient's response to treatment and the likelihood of complications [12]. Additionally, the ALBI grade may provide valuable information regarding tumor size and the extent of liver involvement, which are crucial prognostic factors in CCA [13].

In this systematic review and meta-analysis, our objective is to thoroughly evaluate and consolidate the existing literature on the prognostic significance of ALBI grade in patients with CCA concerning overall and recurrence-free survival. This comprehensive review will provide valuable insights to support clinical decision-making and steer future research in this domain.

Method

The protocol of this systematic review and meta-analysis has been registered in PROSPERO (CRD42022379877). We adhered to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) for conducting this systematic review and meta-analysis [14].

Literature search strategy

The comprehensive literature search using the terms "albumin-bilirubin grade" and "cholangiocarcinoma" was conducted in PubMed, EMBASE, Web of Sciences, and Scopus databases. To ensure a comprehensive search, we excluded the keyword "prognosis" from our database searches and only included papers addressing the predictive value of the mentioned terms. The retrieval period for our search was from the beginning until August 11, 2023. Additionally, we reviewed the references of the included studies and conducted a manual search for relevant articles. The details of our database search strategy are provided in the supplementary material file.

Inclusion and exclusion criteria

The inclusion criteria were the following: (1) patients diagnosed with CCA; (2) assessment of the prognostic value of ALBI grade on overall survival (OS), recurrence-free survival (RFS), progression-free survival (PFS), and recurrence rate; and (3) survival outcomes measured using hazard ratio (HR) with 95% confidence intervals (CIs), Kaplan–Meier curve, or adequate data for calculating HR with 95% CI. (4) papers reporting odds ratios (OR) or median survival were included in our investigation, and their findings are reported separately, although not included in our final meta-analysis. Our study excluded studies that met the following criteria: (1) patients with concurrent CCA and other cancers such as combined hepatocellular-cholangiocarcinoma (cHCC-CCA) or CCA and gallbladder cancer, (2) studies published in languages other than English, (3) case reports, case series, reviews, letters, editorials, comments, and conference papers, (4) research evaluating ALBI fractions instead of the mentioned ALBI grade formula, (5) Studies lacking sufficient data to calculate HR with 95% CI were excluded from our final meta-analysis, but their findings are mentioned if they are relevant to the study's objective.

Study screening, data extraction, and quality assessment

All studies underwent rigorous screening and review (MO, SYA). Two separate reviewers extracted data (NM, IA), and any discrepancies in screening or data extraction were discussed and resolved with a third reviewer. The data extraction process involved capturing study ID (first author's name and publication date), country, sample size, age, ALBI grading, number of patients allocated to each grade, type of cholangiocarcinoma (intrahepatic, extrahepatic, or peri-hilar), treatment strategy, survival outcome (overall survival or recurrence-free survival), model of survival analysis (univariate or multivariate analysis), HR with 95% CI, follow-up period (median), and Newcastle Ottawa Scale (NOS) score. The quality assessment was conducted using the NOS score for cohort studies. Two independent reviewers (NM, IA) evaluated the quality of the included studies using the NOS score, and any inconsistencies in quality assessments were reviewed and resolved with a third reviewer. The NOS assessment comprises three domains: selection, comparability, and result. Each study was assigned a score ranging from 0 to 9, with a score of 6 or higher indicating high quality. The supplementary material provides details on the quality assessment and ranking of each study.

Statistical analysis

In this study, we retrieved the HR and 95% CI from each study to calculate the pooled HR with 95% CI. This helped us assess the predictive usefulness of ALBI grade on OS and RFS in patients with CCA, which is our primary outcome. A HR higher than one is indicative of a poor prognosis. If HR is not specified in any of the studies, it was calculated using survival curves and Tierney's Excel spreadsheet (version 16.49) approach [15]. Given the limited number of studies examining the prognostic significance of ALBI in extrahepatic CCA(ECCA), we restricted our final analysis to those focused on the ICCA population. The heterogeneity between studies was assessed using the Cochran's Q test and I^2 values. $I^2 \leq 25\%$ was considered as low heterogeneity, I^2 between 25 and 50% as moderate heterogeneity, and $I^2 > 50\%$ as high heterogeneity.

Due to statistical and methodological heterogeneity among the included studies, a random-effects model was employed to conduct the meta-analysis. To assess publication bias, funnel plots, Begg's and Egger's tests was used. Sensitivity analysis based on the leave-one out method was employed to evaluate the robustness of the pooled analysis. Furthermore, subgroup meta-analysis based on treatment strategy, sample size, NOS quality score, and ALBI grade was performed. All analyses were conducted using R software (Version 4.3.1) with the *meta* package.

The formula for ALBI grade calculation is demonstrated as log10 bilirubin [mol/L] 0.66 + (albumin [g/L] 0.0852). The ALBI grading is as follows: ALBI grade 1 (ALBI score ≤ 2.60), ALBI grade 2 (ALBI score between 2.60 and 1.39), and ALBI grade 3 (ALBI score > 1.39). In various studies, the cut-off values for high and low ALBI grades are as follows: an ALBI score ≤ 2.70 is considered a low grade, while an ALBI score > 2.70 is regarded as a high grade.

Results

Study search

A total of 761 studies were identified through a comprehensive search of four databases (PubMed, Embase, Web of Science, and Scopus). Following removing duplicate records, 609 studies remained and underwent screening based on their title and abstracts. Subsequently, the full texts of 45 eligible articles were thoroughly reviewed, resulting in the inclusion of 18 relevant studies for our systematic analysis (Fig. 1). Additionally, a manual hand search and examination of reference lists from the included publications were conducted to identify any additional relevant studies.

Studies characteristics

Eighteen studies included in the systematic review involving a total of 4,214 individuals. Fourteen of these studies were conducted in China [16–29], one in the United States [30], one in Japan [31], and two were multinational studies [32, 33]. The sample sizes of the studies ranged from 22 to 706 participants (Table 1). Out of the 18 studies included, four studies did not provide HR with 95% CI to be included in the meta-analysis. Three of these studies presented odds ratios, while one reported median survival concerning ALBI grade and survival outcomes.

Fourteen studies provided direct HR with 95% CI or sufficient data to calculate. Among these studies, one focused on patients with ECCA [25] and the remaining 13 studies, comprising a total of 3,434 individuals, assessed the prognostic value of the ALBI grade in ICCA. As a result, only the ICCA-related studies [16–24, 30–33] were included in the final meta-analysis for OS and RFS. Additional details and the results of the NOS risk of bias assessment can be found in Table 1 and supplementary material.

Pooled overall survival analysis

The prognostic value of ALBI grade in OS for patients with ICCA was assessed using both univariate and multivariate analysis. Univariate analysis was performed

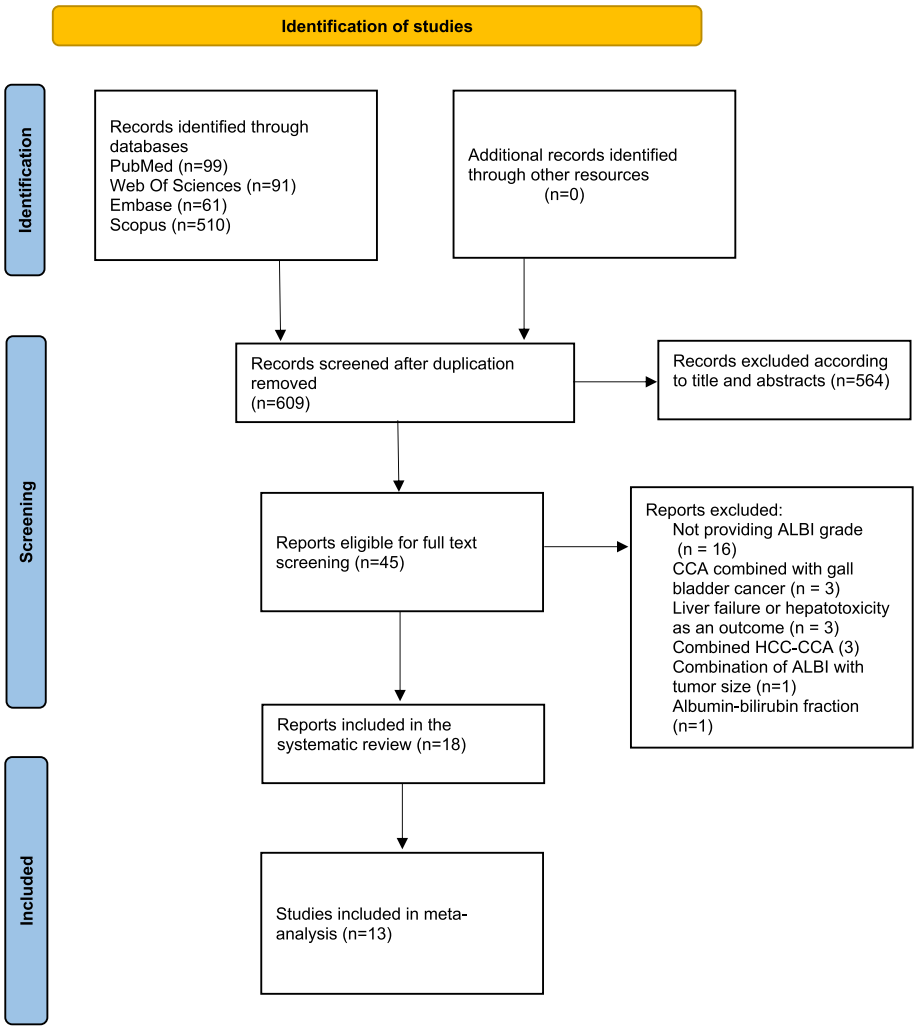

Fig. 1 Study selection flow diagram

on 3,313 subjects. The univariate results showed that a higher ALBI grade is associated with worse outcomes in terms of OS (HR = 1.90, 95%CI: 1.65–2.19, $P < 0.01$, $I^2 = 46\%$, $P_{heterogeneity} = 0.03$) (Fig. 2A). All comparisons of ALBI grades had a negative impact. The best predictive value, however, was found when comparing grade 2 vs grade 1, with an HR of 2.2 (95% CI: 1.83–2.64, $P < 0.01$) (Fig. 2A).

A total of 2,340 patients with ICCA were included in the multivariate analysis. The multivariate analysis revealed that patients with higher ALBI grades had poorer survival outcomes (HR = 1.88, 95% CI: 1.41–2.52, $P < 0.01$, $I^2 = 59\%$, $P_{heterogeneity} = 0.01$) (Fig. 2B). Similar to the univariate analysis, the comparison of ALBI grade 2 vs grade 1 was the strongest predictor among other ALBI grade comparisons in the multivariate analysis (HR = 2.14, 95% CI: 1.50–3.05, $P < 0.01$).

Pooled recurrence-free analysis

A total of 720 patients were included in the study to assess the predictive value of ALBI grade for RFS. Univariate analysis revealed a significant association between higher ALBI grade and recurrence in patients with ICCA (HR = 1.63, 95% CI: 1.36–1.97, $P < 0.01$, $I^2 = 0\%$, $P_{heterogeneity} = 0.45$). It is worth noting that no studies reported conducting multivariate analysis for RFS; only pooled univariate analysis was performed (Fig. 3).

Subgroup analysis

A subgroup meta-analysis was conducted in univariate and multivariate OS analyses based on treatment options, sample size, NOS score, and ALBI grading. In a subgroup study focusing on ALBI, we found that any comparison of ALBI grading effectively predicts survival in patients with ICCA. However, comparing ALBI grade 2 vs. grade 1 yielded better outcomes and is

Table 1 Characteristics of studies included in the systematic review

Study ID	*Country*	*Population (M/F)*	*Age*	*Type of CCA*	*ALBI* **1/2/3**	*Treatment*	*Survival analysis*	*HR (95CI)*	*Follow-up* **(Median)**	*NOS Score*
D I. Tsilimigras [33] 2019	Multicenter	706 (419/278)	57.9[1] (59.4–66)	ICCA	1:453 2: 231 3:22	Surgery	OS (Bi) 2–3 vs 1	1.47 (1.17- 1.84)	20.7 (10.8–39.9)	9
							OS (M)	1.36 (1.04- 1.78)		
KL Xing [16] **2020 (Training cohort)**	China	178 (119/59)	>60 = 58	ICCA	1:121 2:55 3:2	Surgery	PRS (U) 2 vs 1	2.42 (2.53- 3.81)	22.8 (1.2–110.8)	8
							PRS (M) 2 vs 1	2.54 (1.56- 4.14)		
							PRS (U) 3 vs 1	3.39 (0.81–14.14)		
							PRS (M) 3 vs 1	9.67 (1.89–49.33)		
C Xu [17] **2019**	China	121 (102/19)	MWA 54.5 ± 9.3[2] Surgery 53.9 ± 17.5[2]	ICCA	1:47 2:9	MWA and surgery	OS (M) 2 vs 1	2.36 (0.98- 3.77)	NA	7
Q Li [18] **2021 (Training set)**	China	373 (180/193)	>55 = 224	ICCA	H:180 L:193	Surgery	OS (U) H vs L	1.95 (1.48–2.55)	NA	8
							RFS (U) H vs L	1.77 (1.40–2.24)		
Q Li [18] **2021 (Testing set)**	China	163 (NA)	NA	ICCA	NA	Surgery	OS (U) (survival curve) H vs L	1.89[3] (1.11–3.22)	NA	8
							RFS (U) (survival curve) H vs L	1.83[3] (1.17–2.86)		
JY Ni [19] **2019**	China	78 (57/21)	59.6 ± 10[2]	ICCA	1:39 2:39	MWA	OS (U) 2 vs 1	3.92 (1.37–11.23)	22.7 (1–86.7)	9
							OS (M) 2 vs 1	9.56 (1.58–58.00)		
							RFS (U) 2 vs 1	1.01 (0.40–2.57)		
							RFS (M) 2 vs 1	1.38 (0.38–5.06)		
S Kaneko [31] **2021**	Japan	83 (48/35)	72 (44–88)[1]	ICCA	1:34 2:44 3:5	Surgery	OS (U) H vs L	4.31[4] (2.03- 9.07)	NA	7
							OS (M) H vs L	4.78[4] (1.51- 15.15)		

Table 1 (continued)

Study ID	*Country*	*Population (M/F)*	*Age*	*Type of CCA*	*ALBI* **1/2/3**	*Treatment*	*Survival analysis*	*HR (95CI)*	*Follow-up* **(Median)**	*NOS Score*
H Li [20] **2020 (Derivation cohort)**	China	477 (227/250)	58 (49.5–64)[1]	ICCA	1:387 2:90	Surgery	OS (U) (survival curve) 2 vs 1	1.82[3] (1.33–2.49)	NA	9
							OS (M)	1.40 (1.01–1.93)		
H Li [20] **2020 (Validation cohort)**	China	143 (83/60)	59 (51–67)[1]	ICCA	1:103 2:40	Surgery	OS (U) (survival curve) 2 vs 1	2.38[3] (1.44–3.96)	NA	9
							OS (M)	1.91 (1.12–3.27)		
H Yang [21] **2021**	China	52 (39/13)	59.6 ± 10[2]	ICCA	1:27 2:25	MWA	OS (U) 2 vs 1	3.92 (1.37–11.23)	21.7 (3.2–121.7)	8
							OS (M) 2 vs 1	8.23 (1.58–58.00)		
							RFS (U) 2 vs 1	1.01 (0.40–2.57)		
MM Munir [32] 2023	Multicenter	502 (312/190)	NA	ICCA	H:142 L:360	Surgery	OS (U) H vs L	1.51 0.007 (1.12–2.03)	39.9 (35.6–44.1)	9
							OS (M) H vs L	1.2 0.376 (0.8–1.79)		
J Zhu [22] **2023 (Training cohort)**	China	406 (203/203)	58 (50–65)[1]	ICCA	1: 312 2–3: 94	Surgery	OS (U) 2–3 vs 1	1.8 (1.42–2.28)	30 (3–126)	7
J Tan [23] **2023 (Discovery cohort)**	China	76 (48/28)	56.1(10.1)[2]	ICCA	1: 36 2–3: 40	Multiple	OS (U) 2–3 vs 1	1.33 0.432 (0.65–2.7)	19.1	7
A Azar [30] **2020**	USA	22 (7/15)	62.1(13.1)[2]	ICCA	1:14 2:7	Multiple	OS (U) 2 vs 1 (survival curve)	1.11[3] (0.41- 3.06)	9	5
Z Ye [24] **2023**	China	54 (28/26)	64 (40–84)[1]	ICCA	1: 29 2: 25	Multiple	OS 2 vs 1 (survival curve)	1.61[3] (0.73- 3.52)	10.7 (7.8–13.6)	5
							RFS 2 vs 1 (survival curve)	1.24 [3] (0.71- 2.15)		
Y Wang[6] [10] **2018**	China	109 (71- 38)	68.9 (11.1)[2]	ECCA	1–2:47 3:62	PTBS + I^{125}	OS (U) 3 vs 1–2	1.72 (1.10–2.70)	NA	9
							OS (M) 3 vs 1–2	1.65 (1.04–2.61)		

Table 1 (continued)

Study ID	*Country*	*Population (M/F)*	*Age*	*Type of CCA*	*ALBI* **1/2/3**	*Treatment*	*Survival analysis*	*HR (95CI)*	*Follow-up* **(Median)**	*NOS Score*
W Wang[6] [26] **2023**	China	213 (152/61)	<60 = 89	Perihilar and distal CCA	NA	Multiple	OS (U)	1.71[5] (1.29–2.26)	NA	6
							OS (M)	1.41[5] (1.01–1.98)		
B Quan[6] [27] **2022 (training set)**	China	289 (173/116)	<60 = 168	Primary CCA	NA	Surgery	DSS (U) 2 vs 1	1.54[5] (1.05–2.25)	NA	7
							DSS (U) 3 vs 1	4.47[5] (1.81–11.03)		
							DSS (M) 2 vs 1	0.86[5] (0.51–1.43)		
							DSS (M) 3 vs 1	1.52[5] (0.47–4.86)		
Z BO[6] [28] **2023**	China	127 (6760)	63.8 (10.4)[2]	ICCA	<-2.6: 73 ≥-2.6: 54	Surgery	Early recurrence (U)	1.26[5] (0.62–2.58)	NA	7
M Deng[6] [22] **2022**	China	42 (28/14)	55.5 (10.5)[2]	ICCA	NA	Multiple	Media survival 2 vs 1 (14.7 vs 19.3 months)		12.1 (9.9–14.3)	6
							PFS 2 vs 1 (6.9 vs 13.6 months)			

CCA cholangiocarcinoma, *ICCA* intrahepatic cholangiocarcinoma, *OS* overall survival, *U* univariate analysis, *M* multivariate analysis, *Bi* bivariate analysis, *PRS* progression-free survival, *RFS* recurrence-free survival, *DSS* disease-specific survival, *MWA* microwave ablation, *H* high, *L* low, *NA* not available, *PTBS* percutaneous transhepatic biliary stenting, *I* iodine

[1] Expressed as median (IQR)

[2] Expressed as mean ± SD

[3] Calculated from survival curve

[4] Converted from low vs high ALBI

[5] Odds ratio

[6] Not eligible for the final meta-analysis

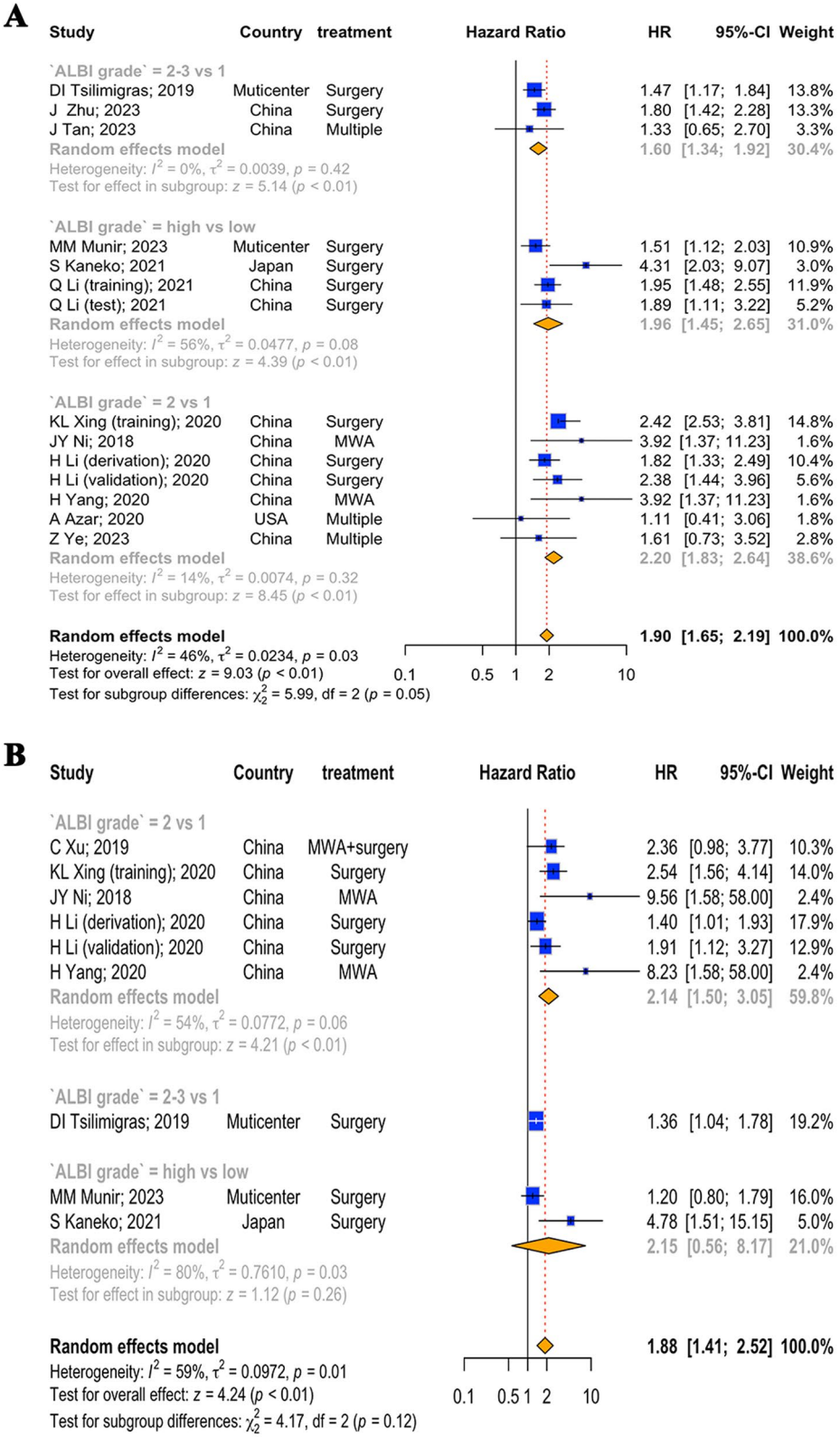

Fig. 2 Meta-analysis forest plots for prognostic value of ALBI grade in overall survival in univariate analysis (**A**), multivariate analysis (**B**), and subgroup analysis of ALBI grade

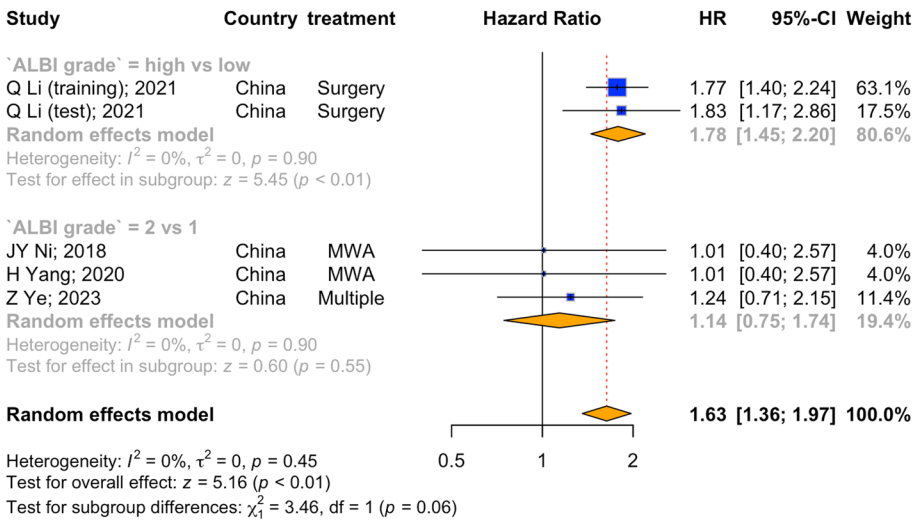

Fig. 3 Meta-analysis forest plots for prognostic value of ALBI grade in recurrence-free survival in univariant analysis, and subgroup analysis of ALBI grade

considered clinically superior to other grade comparisons. Furthermore, we demonstrated that using ALBI for ICCA survival prediction is not limited by treatment plans, as ALBI has shown predictive value across different treatment methods. Additional information on the subgroup analysis can be found in Table 2, and plots illustrating the subgroup analysis are provided in the supplementary material.

Publication bias and sensitivity analysis

In the analysis of OS univariate (Egger's test $p=0.502$, Begg's test $p=0.442$) and RFS univariate (Egger's test $p=0.051$, Begg's test $p=0.19$), publication bias was not taken into account. However, publication bias was observed solely in the multivariate analysis of OS (Egger's test $p=0.001$, Begg's test $p=0.046$). Based on the sensitivity analysis, omitting each study from the pooled analysis, did not make significant changes in the overall effect size. Details of heterogeneity, sensitivity analysis,

Table 2 Subgroup analysis of univariate and multivariate overall survival

Stratified analysis	Number of studies in univariate analysis	HR with 95% CI	*P* value	I^2	Number of studies in multivariate analysis	HR with 95% CI	*P* value	I^2
ALBI grade								
2 vs 1	7	2.20 (1.83–2.64)	< 0.01	14%	6	2.14 (1.50–3.05)	< 0.01	54%
High vs low	4	1.96 (1.45–2.65)	< 0.01	56%	2	2.15 (0.56–8.17)	0.26	80%
2–3 vs 1	3	1.60 (1.34–1.92)	< 0.01	0	1	1.36 (1.04–1.78)		
Treatment								
Surgery	9	1.91 (1.64–2.22)	< 0.01	56%	6	1.63 (1.26–2.11)	< 0.01	54%
Multiple	3	1.37 (0.86–2.18)	0.19	0				
MWA	2	3.92 (1.86–8.25)	< 0.01	0	2	8.87 (2.48–31.71)	< 0.01	0
MWA + surgery					1	2.36 (0.98–3.77)		
Sample size								
Over 200	5	1.69 (1.50–1.90)	< 0.01	0	3	1.34 (1.11–1.61)	< 0.01	0
Below 200	9	2.32 (1.98–2.72)	< 0.01	24%	6	2.56 (1.90–3.45)	< 0.01	17%
Quality score								
≥ 8 score	9	1.93 (1.63–2.28)	< 0.01	53%	7	1.68 (1.28–2.20)	< 0.01	59%
< 8 score	5	1.84 (1.29–2.62)	< 0.01	42%	2	2.86 (1.55–5.29)	< 0.01	7%

MWA Microwave ablation

publication bias tests and funnel plots are included in the supplementary materials.

Discussion

Due to the limited research on prognostic factors in CCA and its unpredictable nature, it is necessary to develop and assess additional prognostic markers to enhance patient management. This study represents the first systematic review and meta-analysis evaluating the predictive value of ALBI grade in CCA patients. A total of 18 papers were included in this study, with 13 of them forming the basis of the meta-analysis. Higher ALBI grade consistently correlates with poorer prognosis in individuals with ICCA, regardless of the comparison technique used (2 versus 1, high versus low, three versus 2–1). However, comparing ALBI grades 2 and 1 provides better prognostic value for both OS and RFS outcomes and is, therefore, the recommended approach in clinical practice. ALBI grade, a novel and straightforward technique for assessing hepatic function, has shown prognostic relevance in diseases such as HCC, acute on chronic liver failure, gastrointestinal bleeding, and primary biliary cirrhosis [11, 34]. ALBI grade was indicated as a non-invasive marker to diagnose liver fibrosis. ALBI grade showed a good ability to differentiate liver fibrosis grade 3 from 2, and grade 4 from 3, in patients with chronic hepatitis C [35]. In a study among 3,495 patients with HCC, ALBI grade was associated with liver damage degree, as determined by Liver Cancer Study Group of Japan (LCSGJ), which is based on serum albumin, bilirubin, prothrombin time, ascites, and indocyanine green retention rate after 15 min (ICG-R15). In this study, most patients with ALBI grade 1 showed ICG-R15 level < 30%, and had liver damage grade A. Most patients with ALBI grade 2 and 3 had a liver damage grade B and C, respectively. None of the patients in ALBI grade 1 had liver damage grade 3 and only one patient in ALBI grade 3 had liver damage grade A [36]. Several meta-analyses have demonstrated that ALBI grade could be a valuable predictive factor in patients with HCC [37–39]. The Child–Pugh classification is a well-established scoring system for evaluating hepatic function and the prognosis of liver diseases. However, subjective assessment of ascites and hepatic encephalopathy can affect the accuracy of the Child–Pugh system [10]. In a systematic review conducted by Ying Peng et al. to compare ALBI versus Child–Pugh in predicting the outcome of patients with HCC, ALBI grade outperformed Child–Pugh grade in predicting mortality, postoperative liver failure, and HCC prognosis, while Child–Pugh grade only predicted post-progression survival [40]. Both ALBI grade and Child-Turcotte-Pugh (CTP), showed similar prognostic value in patients with HCC after stereotactic body radiation therapy in CTP class A. However, both ALBI grade and CTP score showed no predictive value in patients with CTP class B, which needs to be further validated in future studies with more population [41]. In a study among 1,120 HCC patients with renal insufficiency, ALBI grade showed a strong prognostic value with HR of 1.43 for grade 2 and 2.36 for grade 3, and was indicated as the most informative and homogenous predictive marker when compared with other liver functional reserve models, such as model for end stage liver disease 3.0 (MELD 3.0) and platelet-ALBI grade [42]. ALBI grade also has shown promising results in predicting survival in conditions such as cirrhosis. In 398 patients with chronic hepatitis B-related liver cirrhosis, the ALBI grade was an independent predictor of liver-related mortality with HR of 3.15 (95% CI; 2.03–4.86), and outperformed MELD and MELD-Na [43]. ALBI grade was also a good prognostic tool in cirrhotic patients with upper gastrointestinal bleeding, demonstrating a better performance in predicting 30 days mortality compared with MELD and Child–Pugh [44]. Some of the studies included in our analysis also compared the prognostic value of ALBI grade versus Child–Pugh grade in patients with ICCA. ALBI grade also demonstrated a stronger predictive value than the Child–Pugh grade in these studies [18–21]. This may be attributed to the fact that the Child–Pugh grading system includes subjective assessments such as ascites and hepatic encephalopathy. Additionally, Child–Pugh was initially designed for patients with cirrhosis, which is only present in a small population of patients with ICCA [20]. Therefore, ALBI grade is considered more reliable than Child–Pugh grade for predicting outcomes in ICCA patients, especially in those without significant hepatic impairment symptoms. ALBI grade is also not influenced by subjective assessment and is easier to use, as it only requires albumin and bilirubin serum levels. Nonetheless, further research comparing ALBI grade to Child–Pugh grade is needed to reach a more definitive conclusion regarding their predictive utility in patients with ICCA and other types of cholangiocarcinoma.

In a systematic review and meta-analysis evaluating prognostic factors for ICCA, the main prognostic factors were lymph node metastasis (HR: 2.09, 95%CI:1.80–2.43), vascular invasion (HR: 1.87, 95%CI:1.44–2.42), and multiple tumors (HR: 1.7, 95%CI:1.43–2.02). Other mentioned factors, including poor tumor differentiation, positive surgical margin, and tumor size, did not show higher clinical usefulness compared with mentioned factors [45]. Regarding peri-hilar CCA, distant and lymph node metastasis, vascular involvement, T3 or T4-stage, poor tumor differentiation, and perineural involvement were associated with poorer survival outcomes. Other factors such as tumor size, CA 19–9, and CEA were

also associated with poor survival outcomes but were not as significant as those mentioned factors [46, 47]. Perineural invasion, lymph node involvement, resection margin status, and tumor differentiation were also associated with worse survival outcomes in distal CCA [48]. Across different types of CCA, we see differences in prognostic factors, implying different specific characteristics of these types of cancers. However, it is noteworthy that the investigated factors were not similar in the mentioned systematic reviews, each focusing on specific factors. While our study did not specifically focus on a particular type of CCA and we did not restrict our search to any specific type of CCA. Only one study included ECCA patients. Therefore, evaluating ALBI was limited to studies on ICCA in our meta-analysis. As a result of our analysis, ALBI could also be considered as one of the important prognostic factors in ICCA. In the mentioned study among ECCA, higher ALBI grade was associated with worse outcome. This study further evaluated the prognostic value of ALBI grade in distal CCA and hilar CCA, and found that ALBI grade was a significant predictor of OS in both types of ECCA [25]. However, extensive studies evaluating ALBI alongside the mentioned factors in the different types of cholangiocarcinoma are needed to have concrete conclusions.

Inflammation plays a critical role in the tumor microenvironment, and systemic inflammation has been associated with tumor growth [49]. Recently, new inflammatory markers such as the neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) have been proposed as indicators of systemic inflammation and have been linked to cancer progression [50]. Hongxia Cui et al. reviewed 18 cohort studies involving 4123 participants to evaluate the predictive significance of NLR, PLR, and LMR in patients with ICCA. Their findings showed that only a high preoperative NLR was associated with poor OS and RFS (HR = 1.04, 95% CI: 1.01–1.07, and HR = 1.29, 95% CI: 1.04–1.60, respectively) [51]. ALBI is also a novel prognostic tool and as a result of our study, ALBI demonstrated a stronger association with OS and RFS compared to NLR (HR = 1.90, 95%CI: 1.65–2.19 and HR = 1.63, 95%CI: 1.36–1.97, respectively). Therefore, ALBI has a better prognostic value for ICCA patients compared to NLR. However, further research is needed to directly compare these two prognostic markers in the same group of patients in order to reach definitive conclusions. It is also recommended to combine these markers to assess the predictive capacity of integrating ALBI with the aforementioned inflammatory markers. According to Hao Lou's research, the combination of ALBI and NLR has a stronger predictive value in HCC than either ALBI or NLR alone [52].

This study has discovered that a higher ALBI grade is associated with both OS and RFS in ICCA. Our findings remained statistically significant after conducting treatment subgroup analysis, indicating that ALBI is a reliable prognostic indicator regardless of the chosen treatment options. Compared to Child–Pugh and new inflammatory markers (NLR, PLR, and LMR), previous studies have shown that ALBI exhibits a more substantial predictive value. However, further research is necessary to compare various predictors within the same patient group before drawing definitive conclusions. ALBI proves to be a valid predictor of survival in ICCA patients and could be effectively utilized in clinical practice alongside tumor stage, metastasis status, and histological grade to enhance patient management and survival prediction. We also recommend conducting additional studies to evaluate ALBI's prognostic value and assess other risk factors using machine learning and nomogram approaches for more accurate survival prediction. Furthermore, as observed in previous studies [16, 53], combining ALBI with different prognostic values has proven beneficial in survival prediction. Regrettably, there is a scarcity of studies exploring these approaches, and more research is indispensable before they can be incorporated into clinical decision-making.

Strengths and limitations

There are several limitations to be addressed in this study. Firstly, it is essential to mention that all the studies included in this systematic review were retrospective, and only a few of them presented hazard ratios (HR) with a 95% confidence interval (CI) in a multivariate model. Secondly, out of the 18 studies, eight studies did not provide direct HR with a 95% CI. From the remaining four studies, we were able to calculate HR with a 95% CI, while the other four studies lacked sufficient data for this calculation. Thirdly, it is worth noting that studies emphasizing the predictive value of ALBI have mainly focused on ICCA. Although, our search was not restricted to a specific type of CCA, only one of the included studies investigated the prognostic value of ALBI in ECCA. Given that the majority of patients in our systematic review had ICCA and only one study included patients with ECCA, the final meta-analysis was performed among patients with ICCA. ALBI grade was also considered a significant predictor of OS in ECCA patients. Although, more studies and participants are needed to have a concrete conclusion.

Conclusion

This systematic review and meta-analysis identified the ALBI grade as a robust predictor of cholangiocarcinoma, particularly ICCA. Higher ALBI grade correlated with

shorter OS and RFS in ICCA patients. The utilization of ALBI grade in clinical settings can enhance patient care management. We recommend conducting additional large-scale trials, especially focusing on patients with different types of CCA.

Abbreviations

ALBI	Albumin-bilirubin grade
CCA	Cholangiocarcinoma
ICCA	Intrahepatic cholangiocarcinoma
ECCA	Extrahepatic cholangiocarcinoma
HCC	Hepatocellular carcinoma
cHCC-CCA	Combined Hepatocellular-cholangiocarcinoma
CI	Confidence Intervals
HR	Hazard Ratio
OR	Odds Ratio
OS	Overall survival
RFS	Recurrence-free survival
PFS	Progression-free survival
NOS	Newcastle Ottawa Scale
GIB	Gastrointestinal bleeding
PBC	Primary biliary cirrhosis
NLR	Neutrophil-lymphocyte ratio
PLR	Platelet-lymphocyte ratio
LMR	Lymphocyte-monocyte ratio

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Author contribution Study conception: MOK Search strategy and study screening: MOK, SYA Data collection: NM, IA Quality assessment: NM, IA Meta-analysis: HG, MOK Manuscript drafting: MOK, SYA, HG, NM, IA Manuscript editing: MOK, HG, SYA.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics and approval and consent to participant
As a systematic review and meta-analysis, our study did not require any human participation and, referral to our ethics committee.

Consent for publication
Not applicable.

Competing of interest
All authors declare no competing of interest.

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